TARGETED CHROMOSOMAL GENOMIC ALTERATIONS WITH MODIFIED SINGLE STRANDED OLIGONUCLEOTIDES

Field Of The Invention

The technical field of the invention is oligonucleotide-directed repair or alteration of genetic information using novel chemically modified oligonucleotides. Such genetic information is preferably from a eukaryotic organism, i.e. a plant, animal or fungus.

Background Of The Invention

A number of methods have been developed specifically to alter the sequence of an isolated DNA in addition to methods to alter directly the genomic information of various plants, fungi and animals, including humans ("gene therapy"). The latter methods generally include the use of viral or plasmid vectors carrying nucleic acid sequences encoding partial or complete portions of a particular protein which is expressed in a cell or tissue to effect the alteration. The expression of the particular protein then results in the desired phenotype. For example, retroviral vectors containing a transgenic DNA sequence allowing for the production of a normal CFTR protein when administered to defective cells are described in U.S. Patent 5,240,846. Others have developed different "gene therapy vectors" which include, for example, portions of adenovirus (Ad) or adeno-associated virus (AAV), or other viruses. The virus portions used are often long terminal repeat sequences which are added to the ends of a transgene of choice along with other necessary control sequences which allow expression of the transgene. See U.S. Patents 5,700,470 and 5,139,941. Similar methods have been developed for use in plants. See, for example, U.S. Patent 4,459,355 which describes a method for transforming plants with a DNA vector and U.S. Patent 5,188,642 which describes cloning or expression vectors containing a transgenic DNA sequence which when expressed in plants confers resistance to the herbicide glyphosate. The use of such transgene vectors in any eukaryotic organism adds one or more exogenous copies of a gene, which gene may be foreign to the host, in a usually random fashion at one or more integration sites of the organism's genome at some frequency. The gene which was originally present in the genome, which may be a normal allelic variant, mutated, defective, and/or functional, is retained in the genome of the host.

These methods of gene correction are problematic in that complications which can compromise the health of the recipient, or even lead to death, may result. One such problem is that insertion of exogenous nucleic acid at random location(s) in the genome can have deleterious effects. Another problem with such systems includes the addition of unnecessary and unwanted genetic material to the genome of the recipient, including, for example, viral or other vector remnants, control sequences required to allow production of the transgene protein, and reporter genes or resistance markers. Such remnants and added sequences may have presently unrecognized consequences, for example, involving genetic rearrangements of the recipient genomes. Other problems associated with these types of traditional gene therapy methods include autoimmune suppression of cells expressing an inserted gene due to the presence of foreign antigens. Concerns have also been raised with consumption, especially by humans, of plants containing exogenous genetic material.

More recently, simpler systems involving poly- or oligo- nucleotides have been described for use in the alteration of genomic DNA. These chimeric RNA-DNA oligonucleotides, requiring contiguous RNA and DNA bases in a double-stranded molecule folded by complementarity into a double hairpin conformation, have been shown to effect single basepair or frameshift alterations, for example, for mutation or repair of plant or animal genomes. See, for example, WO 99/07865 and U.S. Patent 5,565,350. In the chimeric RNA-DNA oligonucleotide, an uninterrupted stretch of DNA bases within the molecule is required for sequence alteration of the targeted genome while the obligate RNA residues are involved in complex stability. Due to the length, backbone composition, and structural configuration of these chimeric RNA-DNA molecules, they are expensive to synthesize and difficult to purify. Moreover, if the RNA-containing strand of the chimeric RNA-DNA oligonucleotide is designed so as to direct gene conversion, a series of mutagenic reactions resulting in nonspecific base alteration can result. Such a result compromises the utility of such a molecule in methods designed to alter the genomes of plants and animals, including in human gene therapy applications.

Alternatively, other oligo- or poly- nucleotides have been used which require a triplex forming, usually polypurine or polypyrimidine, structural domain which binds to a DNA helical duplex through Hoogsteen interactions between the major groove of the DNA duplex and the oligonucleotide. Such oligonucleotides may have an additional DNA reactive moiety, such as psoralen, covalently linked to the oligonucleotide. These reactive moieties function as effective intercalation agents, stabilize the formation of a triplex and can be mutagenic. Such agents may be required in order to stabilize the triplex forming domain of the oligonucleotide with the DNA double helix if the Hoogsteen interactions from the oligonucleotide/target base composition are insufficient. See, e.g., U.S. Patent 5,422,251. The utility of

these oligonucleotides for directing gene conversion is compromised by a high frequency of nonspecific base changes.

In more recent work, the domain for altering a genome is linked or tethered to the triplex forming domain of the bi-functional oligonucleotide, adding an additional linking or tethering functional domain to the oligonucleotide. See, e.g., Culver et al., Nature Biotechnology 17: 989-93 (1999). Such chimeric or triplex forming molecules have distinct structural requirements for each of the different domains of the complete poly- or oligo-nucleotide in order to effect the desired genomic alteration in either episomal or chromosomal targets.

Other genes, e.g. CFTR, have been targeted by homologous recombination using duplex fragments having several hundred basepairs. See, e.g., Kunzelmann et al., Gene Ther. 3:859-867 (1996). Early experiments to mutagenize an antibiotic resistance indicator gene by homologous recombination used an unmodified DNA oligonucleotide with no functional domains other than a region of complementary sequence to the target. See Campbell et al., New Biologist 1: 223-227 (1989). These experiments required large concentrations of the oligonucleotide, exhibited a very low frequency of episomal modification of a targeted exogenous plasmid gene not normally found in the cell and have not been reproduced. However, as shown in the examples herein, we have observed that an unmodified DNA oligonucleotide can convert a base at low frequency which is detectable using the assay systems described herein.

Artificial chromosomes can be useful for the screening purposed identified herein. These molecules are man-made linear or circular DNA molecules constructed from essential cis-acting DNA sequence elements that are responsible for the proper replication and partitioning of natural chromosomes (Murray et al., 1983). The essential elements are: (1) Autonomous Replication Sequences (ARS), (2) Centromeres, and (3) Telomeres.

Yeast artificial chromosomes (YACs) allow large genomic DNA to be modified and used for generating transgenic animals [Burke et al., Science 236:806; Peterson et al., Trends Genet. 13:61 (1997); Choi, et al., Nat. Genet., 4:117-223 (1993), Davies, et al., Biotechnology 11:911-914 (1993), Matsuura, et al., Hum. Mol. Genet., 5:451-459 (1996), Peterson et al., Proc. Natl. Acad. Sci., 93:6605-6609 (1996); and Schedl, et al., Cell, 86:71-82 (1996)]. Other vectors also have been developed for the cloning of large segments of mammalian DNA, including cosmids, and bacteriophage P1 [Sternberg et al., Proc. Natl. Acad. Sci. U.S.A., 87:103-107 (1990)]. YACs have certain advantages over these alternative large capacity cloning vectors [Burke et al., Science, 236:806-812 (1987)]. The

maximum insert size is 35-30 kb for cosmids, and 100 kb for bacteriophage P1, both of which are much smaller than the maximal insert for a YAC.

An alternative to YACs are E. coli based cloning systems based on the E. coli fertility factor that have been developed to construct large genomic DNA insert libraries. They are bacterial artificial chromosomes (BACs) and P-1 derived artificial chromosomes (PACs) [Mejia et al., Genome Res. 7:179-186 (1997); Shizuya et al., Proc. Natl. Acad. Sci. 89:8794-8797 (1992); Ioannou et al., Nat. Genet., 6:84-89 (1994); Hosoda et al., Nucleic Acids Res. 18:3863 (1990)]. BACs are based on the E. coli fertility plasmid (F factor); and PACs are based on the bacteriophage P1. These vectors propagate at a very low copy number (1-2 per cell) enabling genomic inserts up to 300 kb in size to be stably maintained in recombination deficient hosts. Furthermore, the PACs and BACs are circular DNA molecules that are readily isolated from the host genomic background by classical alkaline lysis [Birnboim et al., Nucleic Acids Res. 7:1513-1523 (1979].

Oligonucleotides designed for use in the alteration of genetic information are significantly different from oligonucleotides designed for antisense approaches. For example, antisense oligonucleotides are perfectly complementary to and bind an mRNA strand in order to modify expression of a targeted mRNA and are used at high concentration. As a consequence, they are unable to produce a gene conversion event by either mutagenesis or repair of a defect in the chromosomal DNA of a host genome. Furthermore, the backbone chemical composition used in most oligonucleotides designed for use in antisense approaches renders them inactive as substrates for homologous pairing or mismatch repair enzymes and the high concentrations of oligonucleotide required for antisense applications can be toxic with some types of nucleotide modifications. In addition, antisense oligonucleotides must be complementary to the mRNA and therefore, may not be complementary to the other DNA strand or to genomic sequences that span the junction between intron sequence and exon sequence.

A need exists for simple, inexpensive oligonucleotides capable of producing targeted alteration of genetic material such as those described herein as well as methods to identify optimal oligonucleotides that accurately and efficiently alter target DNA.

Summary Of The Invention

Novel, modified single-stranded nucleic acid molecules that direct gene alteration in plants, fungi and animals are identified and the efficiency of alteration is analyzed both in vitro using a cell-free extract assay and in vivo using a yeast cell system. The alteration in an oligonucleotide of the invention may comprise an insertion, deletion, substitution, as well as any combination of these. Site

specific alteration of DNA is not only useful for studying function of proteins in vivo, but it is also useful for creating animal models for human disease, and in gene therapy. As described herein, oligonucleotides of the invention target directed specific gene alterations in genomic double-stranded DNA cells. The target DNA can be normal, cellular chromosomal DNA, extrachromosomal DNA present in cells in different forms including, e.g., mammalian artificial chromosomes (MACs), PACs from P-1 vectors, yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), plant artificial chromosomes (PLACs), as well as episomal DNA, including episomal DNA from an exogenous source such as a plasmid or recombinant vector. Many of these artificial chromosome constructs containing human DNA can be obtained from a variety of sources, including, e.g., the Whitehead Institute, and are described, e.g., in Cohen et al., Nature 336:698-701 (1993) and Chumakov, et al., Nature 377:174-297 (1995). The target DNA may be transcriptionally silent or active. In a preferred embodiment, the target DNA to be altered is the non-transcribed strand of a genomic DNA duplex.

The low efficiency of gene alteration obtained using unmodified DNA oligonucleotides is believed to be largely the result of degradation by nucleases present in the reaction mixture or the target cell. Although different modifications are known to have different effects on the nuclease resistance of oligonucleotides or stability of duplexes formed by such oligonucleotides (see, e.g., Koshkin et al., J. Am. Chem. Soc., 120:13252-3), we have found that it is not possible to predict which of any particular known modification would be most useful for any given alteration event, including for the construction of gene conversion oligonucleotides, because of the interaction of different as yet unidentified proteins during the gene alteration event. Herein, a variety of nucleic acid analogs have been developed that increase the nuclease resistance of oligonucleotides that contain them, including, e.g., nucleotides containing phosphorothioate linkages or 2'-O-methyl analogs. We recently discovered that single-stranded DNA oligonucleotides modified to contain 2'-O-methyl RNA nucleotides or phosphorothioate linkages can enable specific alteration of genetic information at a higher level than either unmodified single-stranded DNA or a chimeric RNA/DNA molecule. See priority applications incorporated herein in their entirety; see also Gamper et al., Nucleic Acids Research 28: 4332-4339 (2000). We also found that additional nucleic acid analogs which increase the nuclease resistance of oligonucleotides that contain them, including, e.g., "locked nucleic acids" or "LNAs", xylo-LNAs and L-ribo-LNAs; see, for example, Wengel & Nielsen, WO 99/14226; Wengel, WO 00/56748 and Wengel, WO 00/66604; also allow specific targeted alteration of genetic information.

The assay allows for determining the optimum length of the oligonucleotide, optimum sequence of the oligonucleotide, optimum position of the mismatched base or bases, optimum chemical

modification or modifications, optimum strand targeted for identifying and selecting the most efficient oligonucleotide for a particular gene alteration event by comparing to a control oligonucleotide. Control oligonucleotides may include a chimeric RNA-DNA double hairpin oligonucleotide directing the same gene alteration event, an oligonucleotide that matches its target completely, an oligonucleotide in which all linkages are phosphorothiolated, an oligonucleotide fully substituted with 2'-O-methyl analogs or an RNA oligonucleotide. Such control oligonucleotides either fail to direct a targeted alteration or do so at a lower efficiency as compared to the oligonucleotides of the invention. The assay further allows for determining the optimum position of a gene alteration event within an oligonucleotide, optimum concentration of the selected oligonucleotide for maximum alteration efficiency by systematically testing a range of concentrations, as well as optimization of either the source of cell extract by testing different organisms or strains, or testing cells derived from different organisms or strains, or cell lines. Using a series of single-stranded oligonucleotides, comprising all RNA or DNA residues and various mixtures of the two, several new structures are identified as viable molecules in nucleotide conversion to direct or repair a genomic mutagenic event. When extracts from mammalian, plant and fungal cells are used and are analyzed using a genetic readout assay in bacteria, single-stranded oligonucleotides having one of several modifications are found to be more active than a control RNA-DNA double hairpin chimera structure when evaluated using an in vitro gene repair assay. Similar results are also observed in vivo using yeast, mammalian, rodent, monkey, human and embryonic cells, including stem cells. Molecules containing various lengths of modified bases were found to possess greater activity than unmodified single-stranded DNA molecules.

Detailed Description Of The Invention

The present invention provides oligonucleotides having chemically modified, nuclease resistant residues, preferably at or near the termini of the oligonucleotides, and methods for their identification and use in targeted alteration of genetic material, including gene mutation, targeted gene repair and gene knockout. The oligonucleotides are preferably used for mismatch repair or alteration by changing at least one nucleic acid base, or for frameshift repair or alteration by addition or deletion of at least one nucleic acid base. The oligonucleotides of the invention direct any such alteration, including gene correction, gene repair or gene mutation and can be used, for example, to introduce a polymorphism or haplotype or to eliminate ("knockout") a particular protein activity.

The oligonucleotides of the invention are designed as substrates for homologous pairing and repair enzymes and as such have a unique backbone composition that differs from chimeric RNA-

DNA double hairpin oligonucleotides, antisense oligonucleotides, and/or other poly- or oligo-nucleotides used for altering genomic DNA, such as triplex forming oligonucleotides. The single-stranded oligo-nucleotides described herein are inexpensive to synthesize and easy to purify. In side-by-side comparisons, an optimized single-stranded oligonucleotide comprising modified residues as described herein is significantly more efficient than a chimeric RNA-DNA double hairpin oligonucleotide in directing a base substitution or frameshift mutation in a cell-free extract assay.

We have discovered that single-stranded oligonucleotides having a DNA domain surrounding the targeted base, with the domain preferably central to the poly- or oligo-nucleotide, and having at least one modified end, preferably at the 3' terminal region are able to alter a target genetic sequence and with an efficiency that is higher than chimeric RNA-DNA double hairpin oligonucleotides disclosed in US Patent 5,565,350. Oligonucleotides of the invention can efficiently be used to introduce targeted alterations in a genetic sequence of DNA in the presence of human, animal, plant, fungal (including yeast) proteins and in cultured cells of human liver, lung, colon, cervix, kidney, epethelium and cancer cells and in monkey, hamster, rat and mouse cells of different types, as well as embryonic stem cells. Cells for use in the invention include, e.g., fungi including *S. cerevisiae*, *Ustillago maydis* and *Candida albicans*, mammalian, mouse, hamster, rat, monkey, human and embryonic cells including stem cells. The DNA domain is preferably fully complementary to one strand of the gene target, except for the mismatch base or bases responsible for the gene alteration or conversion events. On either side of the preferably central DNA domain, the contiguous bases may be either RNA bases or, preferably, are primarily DNA bases. The central DNA domain is generally at least 8 nucleotides in length. The base(s) targeted for alteration in the most preferred embodiments are at least about 8, 9 or 10 bases from one end of the oligonucleotide.

According to certain embodiments, the termini of the oligonucleotides of the present invention comprise phosphorothioate modifications, LNA backbone modifications, or 2'-O-methyl base analogs, or any combination of these modifications. Oligonucleotides comprising 2'-O-methyl or LNA analogs are a mixed DNA/RNA polymer. These oligonucleotides are, however, single-stranded and are not designed to form a stable internal duplex structure within the oligonucleotide. The efficiency of gene alteration is surprisingly increased with oligonucleotides having internal complementary sequence comprising phosphorothioate modified bases as compared to 2'-O-methyl modifications. This result indicates that specific chemical interactions are involved between the converting oligonucleotide and the proteins involved in the conversion. The effect of other such chemical interactions to produce nuclease resistant termini using modifications other than LNA, phosphorothioate linkages, or 2'-O-methyl analog

incorporation into an oligonucleotide can not yet be predicted because the proteins involved in the alteration process and their particular chemical interaction with the oligonucleotide substituents are not yet known and cannot be predicted.

In the examples, correcting oligonucleotides of defined sequence are provided for correction of genes mutated in human diseases. In the tables of these examples, the oligonucleotides of the invention are not limited to the particular sequences disclosed. The oligonucleotides of the invention include extensions of the appropriate sequence of the longer 120 base oligonucleotides which can be added base by base to the smallest disclosed oligonucleotides of 17 bases. Thus the oligonucleotides of the invention include for each correcting change, oligonucleotides of length 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, or 120 with further single-nucleotide additions up to the longest sequence disclosed. Moreover, the oligonucleotides of the invention do not require a symmetrical extension on either side of the central DNA domain. Similarly, the oligonucleotides of the invention as disclosed in the various tables for correction of human diseases contain phosphorothioate linkages, 2'-O-methyl analogs or LNAs or any combination of these modifications just as the assay oligonucleotides do.

The present invention, however, is not limited to oligonucleotides that contain any particular nuclease resistant modification. Oligonucleotides of the invention may be altered with any combination of additional LNAs, phosphorothioate linkages or 2'-O-methyl analogs to maximize conversion efficiency. For oligonucleotides of the invention that are longer than about 17 to about 25 bases in length, internal as well as terminal region segments of the backbone may be altered. Alternatively, simple fold-back structures at each end of a oligonucleotide or appended end groups may be used in addition to a modified backbone for conferring additional nuclease resistance.

The different oligonucleotides of the present invention preferably contain more than one of the aforementioned backbone modifications at each end. In some embodiments, the backbone modifications are adjacent to one another. However, the optimal number and placement of backbone modifications for any individual oligonucleotide will vary with the length of the oligonucleotide and the particular type of backbone modification(s) that are used. If constructs of identical sequence having phosphorothioate linkages are compared, 2, 3, 4, 5, or 6 phosphorothioate linkages at each end are preferred. If constructs of identical sequence having 2'-O-methyl base analogs are compared, 1, 2, 3 or 4

analogs are preferred. The optimal number and type of backbone modifications for any particular oligonucleotide useful for altering target DNA may be determined empirically by comparing the alteration efficiency of the oligonucleotide comprising any combination of the modifications to a control molecule of comparable sequence using any of the assays described herein. The optimal position(s) for oligonucleotide modifications for a maximally efficient altering oligonucleotide can be determined by testing the various modifications as compared to control molecule of comparable sequence in one of the assays disclosed herein. In such assays, a control molecule includes, e.g., a completely 2'-O-methyl substituted molecule, a completely complementary oligonucleotide, or a chimeric RNA-DNA double hairpin.

Increasing the number of phosphorothioate linkages, LNAs or 2'-O-methyl bases beyond the preferred number generally decreases the gene repair activity of a 25 nucleotide long oligonucleotide. Based on analysis of the concentration of oligonucleotide present in the extract after different time periods of incubation, it is believed that the terminal modifications impart nuclease resistance to the oligonucleotide thereby allowing it to survive within the cellular environment. However, this may not be the only possible mechanism by which such modifications confer greater efficiency of conversion. For example, as disclosed herein, certain modifications to oligonucleotides confer a greater improvement to the efficiency of conversion than other modifications.

Efficiency of conversion is defined herein as the percentage of recovered substate molecules that have undergone a conversion event. Depending on the nature of the target genetic material, e.g. the genome of a cell, efficiency could be represented as the proportion of cells or clones containing an extrachromosomal element that exhibit a particular phenotype. Alternatively, representative samples of the target genetic material can be sequenced to determine the percentage that have acquired the desire change. The oligonucleotides of the invention in different embodiments can alter DNA one, two, three, four, five, six, seven, eight, nine, ten, twelve, fifteen, twenty, thirty, and fifty or more fold more than control oligonucleotides. Such control oligonucleotides are oligonucleotides with fully phosphorothiolated linkages, oligonucleotides that are fully substituted with 2'-O-methyl analogs, a perfectly matched oligonucleotide that is fully complementary to a target sequence or a chimeric DNA-RNA double hairpin oligonucleotide such as disclosed in US Patent 5,565,350.

In addition, for a given oligonucleotide length, additional modifications interfere with the ability of the oligonucleotide to act in concert with the cellular recombination or repair enzyme machinery which is necessary and required to mediate a targeted substitution, addition or deletion event in DNA. For

example, fully phosphorothiolated or fully 2-O-methylated molecules are inefficient in targeted gene alteration.

The oligonucleotides of the invention as optimized for the purpose of targeted alteration of genetic material, including gene knockout or repair, are different in structure from antisense oligonucleotides that may possess a similar mixed chemical composition backbone. The oligonucleotides of the invention differ from such antisense oligonucleotides in chemical composition, structure, sequence, and in their ability to alter genomic DNA. Significantly, antisense oligonucleotides fail to direct targeted gene alteration. The oligonucleotides of the invention may target either the Watson or the Crick strand of DNA and can include any component of the genome including, for example, intron and exon sequences. The preferred embodiment of the invention is a modified oligonucleotide that binds to the non-transcribed strand of a genomic DNA duplex. In other words, the preferred oligonucleotides of the invention target the sense strand of the DNA, i.e. the oligonucleotides of the invention are complementary to the non-transcribed strand of the target duplex DNA. The sequence of the non-transcribed strand of a DNA duplex is found in the mRNA produced from that duplex, given that mRNA uses uracil-containing nucleotides in place of thymine-containing nucleotides.

Moreover, the initial observation that single-stranded oligonucleotides comprising these modifications and lacking any particular triplex forming domain have reproducibly enhanced gene repair activity in a variety of assay systems as compared to a chimeric RNA-DNA double-stranded hairpin control or single-stranded oligonucleotides comprising other backbone modifications was surprising. The single-stranded molecules of the invention totally lack the complementary RNA binding structure that stabilizes a normal chimeric double-stranded hairpin of the type disclosed in U.S. Patent 5,565,350 yet is more effective in producing targeted base conversion as compared to such a chimeric RNA-DNA double-stranded hairpin. In addition, the molecules of the invention lack any particular triplex forming domain involved in Hoogsteen interactions with the DNA double helix and required by other known oligonucleotides in other oligonucleotide dependant gene conversion systems. Although the lack of these functional domains was expected to decrease the efficiency of an alteration in a sequence, just the opposite occurs: the efficiency of sequence alteration using the modified oligonucleotides of the invention is higher than the efficiency of sequence alteration using a chimeric RNA-DNA hairpin targeting the same sequence alteration. Moreover, the efficiency of sequence alteration or gene conversion directed by an unmodified oligonucleotide is many times lower as compared to a control chimeric RNA-DNA molecule or the modified oligonucleotides of the invention targeting the same sequence alteration. Similarly,

molecules containing at least 3 2'-O-methyl base analogs are about four to five fold less efficient as compared to an oligonucleotide having the same number of phosphorothioate linkages.

The oligonucleotides of the present invention for alteration of a single base are about 17 to about 121 nucleotides in length, preferably about 17 to about 74 nucleotides in length. Most preferably, however, the oligonucleotides of the present invention are at least about 25 bases in length, unless there are self-dimerization structures within the oligonucleotide. If the oligonucleotide has such an unfavorable structure, lengths longer than 35 bases are preferred. Oligonucleotides with modified ends both shorter and longer than certain of the exemplified, modified oligonucleotides herein function as gene repair or gene knockout agents and are within the scope of the present invention.

Once an oligomer is chosen, it can be tested for its tendency to self-dimerize, since self-dimerization may result in reduced efficiency of alteration of genetic information. Checking for self-dimerization tendency can be accomplished manually or, more preferably, by using a software program. One such program is Oligo Analyzer 2.0, available through Integrated DNA Technologies (Coralville, IA 52241) (http://www.idtdna.com); this program is available for use on the world wide web at

http://www.idtdna.com/program/oligoanalyzer/
oligoanalyzer.asp.

For each oligonucleotide sequence input into the program, Oligo Analyzer 2.0 reports possible self-dimerized duplex forms, which are usually only partially duplexed, along with the free energy change associated with such self-dimerization. Delta G-values that are negative and large in magnitude, indicating strong self-dimerization potential, are automatically flagged by the software as "bad". Another software program that analyzes oligomers for pair dimer formation is Primer Select from DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715, Phone: (608) 258-7420 (http://www.dnastar.com/products/PrimerSelect.html).

If the sequence is subject to significant self-dimerization, the addition of further sequence flanking the "repair" nucleotide can improve gene correction frequency.

Generally, the oligonucleotides of the present invention are identical in sequence to one strand of the target DNA, which can be either strand of the target DNA, with the exception of one or more targeted bases positioned within the DNA domain of the oligonucleotide, and preferably toward the middle between the modified terminal regions. Preferably, the difference in sequence of the oligonucleotide as compared to the targeted genomic DNA is located at about the middle of the oligonucleotide sequence. In a preferred embodiment, the oligonucleotides of the invention are complementary to the non-transcribed strand of a duplex. In other words, the preferred oligonucleotides target the sense strand of the DNA, i.e.

the oligonucleotides of the invention are preferably complementary to the strand of the target DNA the sequence of which is found in the mRNA.

The oligonucleotides of the invention can include more than a single base change. In an oligonucleotide that is about a 70-mer, with at least one modified residue incorporated on the ends, as disclosed herein, multiple bases can be simultaneously targeted for change. The target bases may be up to 27 nucleotides apart and may not be changed together in all resultant plasmids in all cases. There is a frequency distribution such that the closer the target bases are to each other in the central DNA domain within the oligonucleotides of the invention, the higher the frequency of change in a given cell. Target bases only two nucleotides apart are changed together in every case that has been analyzed. The farther apart the two target bases are, the less frequent the simultaneous change. Thus, oligonucleotides of the invention may be used to repair or alter multiple bases rather than just one single base. For example, in a 74-mer oligonucleotide having a central base targeted for change, a base change event up to about 27 nucleotides away can also be effected. The positions of the altering bases within the oligonucleotide can be optimized using any one of the assays described herein. Preferably, the altering bases are at least about 8 nucleotides from one end of the oligonucleotide.

The oligonucleotides of the present invention can be introduced into cells by any suitable means. According to certain preferred embodiments, the modified oligonucleotides may be used alone. Suitable means, however, include the use of polycations, cationic lipids, liposomes, polyethylenimine (PEI), electroporation, biolistics, microinjection and other methods known in the art to facilitate cellular uptake. According to certain preferred embodiments of the present invention, the isolated cells are treated in culture according to the methods of the invention, to mutate or repair a target gene. Modified cells may then be reintroduced into the organism as, for example, in bone marrow having a targeted gene. Alternatively, modified cells may be used to regenerate the whole organism as, for example, in a plant having a desired targeted genomic change. In other instances, targeted genomic alteration, including repair or mutagenesis, may take place in vivo following direct administration of the modified, single-stranded oligonucleotides of the invention to a subject.

The single-stranded, modified oligonucleotides of the present invention have numerous applications as gene repair, gene modification, or gene knockout agents. Such oligonucleotides may be advantageously used, for example, to introduce or correct multiple point mutations. Each mutation leads to the addition, deletion or substitution of at least one base pair. The methods of the present invention offer distinct advantages over other methods of altering the genetic makeup of an organism, in that only the individually targeted bases are altered. No additional foreign DNA sequences are added to the

genetic complement of the organism. Such agents may, for example, be used to develop plants or animals with improved traits by rationally changing the sequence of selected genes in cultured cells. Modified cells are then cloned into whole plants or animals having the altered gene. See, e.g., U.S. Patent 6,046,380 and U.S. Patent 5,905,185 incorporated hererin by reference. Such plants or animals produced using the compositions of the invention lack additional undesirable selectable markers or other foreign DNA sequences. Targeted base pair substitution or frameshift mutations introduced by an oligonucleotide in the presence of a cell-free extract also provides a way to modify the sequence of extrachromosomal elements, including, for example, plasmids, cosmids and artificial chromosomes. The oligonucleotides of the invention also simplify the production of transgenic animals having particular modified or inactivated genes. Altered animal or plant model systems such as those produced using the methods and oligonucleotides of the invention are invaluable in determining the function of a gene and in evaluating drugs. The oligonucleotides and methods of the present invention may also be used for gene therapy to correct mutations causative of human diseases.

The purified oligonucleotide compositions may be formulated in accordance with routine procedures as a pharmaceutical composition adapted for bathing cells in culture, for microinjection into cells in culture, and for intravenous administration to human beings or animals. Typically, compositions for cellular administration or for intravenous administration into animals, including humans, are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anaesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients will be supplied either separately or mixed together in unit dosage form, for example, as a dry, lyophilized powder or water-free concentrate. The composition may be stored in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent in activity units. Where the composition is administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade "water for injection" or saline. Where the composition is to be administered by injection, an ampule of sterile water for injection or saline may be provided so that the ingredients may be mixed prior to administration.

Pharmaceutical compositions of this invention comprise the compounds of the present invention and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable ingredient, excipient, carrier, adjuvant or vehicle.

The oligonucleotides of the invention are preferably administered to the subject in the form of an injectable composition. The composition is preferably administered parenterally, meaning intravenously, intraarterially, intrathecally, interstitially or intracavitarilly. Pharmaceutical compositions of

this invention can be administered to mammals including humans in a manner similar to other diagnostic or therapeutic agents. The dosage to be administered, and the mode of administration will depend on a variety of factors including age, weight, sex, condition of the subject and genetic factors, and will ultimately be decided by medical personnel subsequent to experimental determinations of varying dosage as described herein. In general, dosage required for correction and therapeutic efficacy will range from about 0.001 to 50,000 μg/kg, preferably between 1 to 250 μg/kg of host cell or body mass, and most preferably at a concentration of between 30 and 60 micromolar.

For cell administration, direct injection into the nucleus, biolistic bombardment, electroporation, liposome transfer and calcium phosphate precipitation may be used. In yeast, lithium acetate or spheroplast transformation may also be used. In a preferred method, the administration is performed with a liposomal transfer compound, e.g., DOTAP (Boehringer-Mannheim) or an equivalent such as lipofectin. The amount of the oligonucleotide used is about 500 nanograms in 3 micrograms of DOTAP per 100,000 cells. For electroporation, between 20 and 2000 nanograms of oligonucleotide per million cells to be electroporated is an appropriate range of dosages which can be increased to improve efficiency of genetic alteration upon review of the appropriate sequence according to the methods described herein.

Another aspect of the invention is a kit comprising at least one oligonucleotide of the invention. The kit may comprise an addition reagent or article of manufacture. The additional reagent or article of manufacture may comprise a cell extract, a cell, or a plasmid, such as one of those disclosed in the Figures herein, for use in an assay of the invention.

Brief Description Of The Drawings

Figure 1. *Flow diagram for the generation of modified single-stranded oligonucleotides.* The upper strands of chimeric oligonucleotides I and II are separated into pathways resulting in the generation of single-stranded oligonucleotides that contain (A) 2'-O-methyl RNA nucleotides or (B) phosphorothioate linkages. Fold changes in repair activity for correction of kan^s in the HUH7 cell-free extract are presented in parenthesis. HUH7 cells are described in Nakabayashi et al., Cancer Research 42: 3858-3863 (1982). Each single-stranded oligonucleotide is 25 bases in length and contains a G residue mismatched to the complementary sequence of the kan^s gene. The numbers 3, 6, 8, 10, 12 and 12.5 respectively indicate how many phosphorothioate linkages (S) or 2'-O-methyl RNA nucleotides (R) are at each end of the molecule. Hence oligo 12S/25G contains an all phosphorothioate backbone, displayed as a dotted line. Smooth lines indicate DNA residues, wavy lines indicate 2'-O-methyl RNA

residues and the carat indicates the mismatched base site (G). Figure 1(C) provides a schematic plasmid indicating the sequence of the kan chimeric double-stranded hairpin oligonucleotide (left) and the sequence the tet chimeric double-stranded hairpin oligonucleotide used in other experiments. Figure 1(D) provides a flow chart of a kan experiment in which a chimeric double-stranded hairpin oligonucleotide is used.

Figure 2. *Genetic readout system for correction of a point mutation in plasmid* pK^{s}m4021. A mutant kanamycin gene harbored in plasmid pK^{s}m4021 is the target for correction by oligonucleotides. The mutant G is converted to a C by the action of the oligo. Corrected plasmids confer resistance to kanamycin in *E.coli* (DH10B) after electroporation leading to the genetic readout and colony counts.

Figure 3: *Target plasmid and sequence correction of a frameshift mutation by chimeric and single-stranded oligonucleotides.* (A) Plasmid pT$^{s}\Delta$208 contains a single base deletion mutation at position 208 rendering it unable to confer tet resistance. The target sequence presented below indicates the insertion of a T directed by the oligonucleotides to re-establish the resistant phenotype. (B) DNA sequence confirming base insertion directed by Tet 3S/25G; the yellow highlight indicates the position of frameshift repair.

Figure 4. *DNA sequences of representative kan^{r} colonies.* Confirmation of sequence alteration directed by the indicated molecule is presented along with a table outlining codon distribution. Note that 10S/25G and 12S/25G elicit both mixed and unfaithful gene repair. The number of clones sequenced is listed in parentheses next to the designation for the single-stranded oligonucleotide. A plus (+) symbol indicates the codon identified while a figure after the (+) symbol indicates the number of colonies with a particular sequence. TAC/TAG indicates a mixed peak. Representative DNA sequences are presented below the table with yellow highlighting altered residues.

Figure 5. *Gene correction in HeLa cells.* Representative oligonucleotides of the invention are co-transfected with the pCMVneo($^{-}$)FlAsH plasmid (shown in Figure 9) into HeLa cells. Ligand is diffused into cells after co-transfection of plasmid and oligonucleotides. Green fluorescence indicates gene correction of the mutation in the antibiotic resistance gene. Correction of the mutation results in the expression of a fusion protein that carries a marker ligand binding site and when the fusion protein binds the ligand, a green fluorescence is emitted. The ligand is produced by Aurora Biosciences and can readily diffuse into cells enabling a measurement of corrected protein function; the protein must bind the ligand directly to induce fluorescence. Hence cells bearing the corrected plasmid gene appear green while "uncorrected" cells remain colorless.

Figure 6. *Z-series imaging of corrected cells.* Serial cross-sections of the HeLa cell represented in Figure 5 are produced by Zeiss 510 LSM confocal microscope revealing that the fusion protein is contained within the cell.

Figure 7. *Hygromycin-eGFP target plasmids.* (A) Plasmid pAURHYG(ins)GFP contains a single base insertion mutation between nucleotides 136 and 137, at codon 46, of the Hygromycin B coding sequence (cds) which is transcribed from the constitutive ADH1 promoter. The target sequence presented below indicates the deletion of an A and the substitution of a C for a T directed by the oligonucleotides to re-establish the resistant phenotype. (B) Plasmid pAURHYG(rep)GFP contains a base substitution mutation introducing a G at nucleotide 137, at codon 46, of the Hygromycin B coding sequence (cds). The target sequence presented below the diagram indicates the amino acid conservative replacement of G with C, restoring gene function.

Figure 8. *Oligonucleotides for correction of hygromycin resistance gene.* The sequence of the oligonucleotides used in experiments to assay correction of a hygromycin resistance gene are shown. DNA residues are shown in capital letters, RNA residues are shown in lowercase and nucleotides with a phosphorothioate backbone are capitalized and underlined.

Figure 9. *pAURNeo(-)FlAsH plasmid.* This figure describes the plasmid structure, target sequence, oligonucleotides, and the basis for detection of the gene alteration event by fluorescence.

Figure 10. pYESHyg(x)eGFP plasmid. This plasmid is a construct similar to the pAURHyg(x)eGFP construct shown in Figure 7, except the promoter is the inducible GAL1 promoter. This promoter is inducible with galactose, leaky in the presence of raffinose, and repressed in the presence of dextrose.

The following examples are provided by way of illustration only, and are not intended to limit the scope of the invention disclosed herein.

EXAMPLE 1
Assay Method For Base Alteration And Preferred Oligonucleotide Selection

In this example, single-stranded and double-hairpin oligonucleotides with chimeric backbones (see Figure 1 for structures (A and B) and sequences (C and D) of assay oligonucleotides) are used to correct a point mutation in the kanamycin gene of pK^{s}m4021 (Figure 2) or the tetracycline gene of pT^{s}Δ208 (Figure 3). All kan oligonucleotides share the same 25 base sequence surrounding the target base identified for change, just as all tet oligonucleotides do. The sequence is given in Figures 1C and Figure 1D. Each plasmid contains a functional ampicillin gene. Kanamycin gene function is restored

when a G at position 4021 is converted to a C (via a substitution mutation); tetracycline gene function is restored when a deletion at position 208 is replaced by a C (via frameshift mutation). A separate plasmid, pAURNeo(-)FlAsH (Figure 9), bearing the kan^s gene is used in the cell culture experiments. This plasmid was constructed by inserting a synthetic expression cassette containing a neomycin phosphotransferase (kanamycin resistance) gene and an extended reading frame that encodes a receptor for the FlAsH ligand into the pAUR123 shuttle vector (Panvera Corp., Madison, WI). The resulting construct replicates in *S. cerevisiae* at low copy number, confers resistance to aureobasidinA and constitutively expresses either the Neo+/FlAsH fusion product (after alteration) or the truncated Neo-/FlAsH product (before alteration) from the ADH1 promoter. By extending the reading frame of this gene to code for a unique peptide sequence capable of binding a small ligand to form a fluorescent complex, restoration of expression by correction of the stop codon can be detected in real time using confocal microscopy. Additional constructs can be made to test additional gene alteration events.

We also construct three mammalian expression vectors, pHyg(rep)eGFP, pHyg(Δ)eGFP, pHyg(ins)eGFP, that contain a substitution mutation at nucleotide 137 of the hygromycin-B coding sequence. (rep) indicates a T137➔G replacement, (Δ) represents a deletion of the G137 and (ins) represents an A insertion between nucleotides 136 and 137. All point mutations create a nonsense termination codon at residue 46. We use pHygEGFP plasmid (Invitrogen, CA) DNA as a template to introduce the mutations into the hygromycin-eGFP fusion gene by a two step site-directed mutagenesis PCR protocol. First, we generate overlapping 5' and a 3' amplicons surrounding the mutation site by PCR for each of the point mutation sites. A 215 bp 5' amplicon for the (rep), (Δ) or (ins) was generated by polymerization from oligonucleotide primer HygEGFPf (5'-AATACGACTCACTATAGG-3') to primer Hygrepr (5'GACCTATCCACGCCCTCC-3'), HygΔr (5'-GACTATCCACGCCCTCC-3'), or Hyginsr (5'-GACATTATCCACGCCCTCC-3'), respectively. We generate a 300bp 3' amplicon for the (rep), (Δ) or (ins) by polymerization from oligonucleotide primers Hygrepf (5'-CTGGGATAGGTCCTGCGG-3'), HygΔf (5'-CGTGGATAGTCCTGCGG-3'), Hyginsf (5'-CGTGGATAATGTCCTGCGG-3'), respectively to primer HygEGFPr (5'-AAATCACGCCATGTAGTG-3'). We mix 20 ng of each of the resultant 5' and 3' overlapping amplicon mutation sets and use the mixture as a template to amplify a 523 bp fragment of the Hygromycin gene spanning the KpnI and RsrII restriction endonuclease sites. We use the Expand PCR system (Roche) to generate all amplicons with 25 cycles of denaturing at 94°C for 10 seconds, annealing at 55°C for 20 seconds and elongation at 68°C for 1 minute. We digest 10 μg of vector pHygEGFP and 5 μg of the resulting fragments for each mutation with KpnI and RsrII (NEB) and gel purify the fragment for enzymatic ligation. We ligate each mutated insert into pHygEGFP vector at 3:1 molar ration using T4

DNA ligase (Roche). We screen clones by restriction digest, confirm the mutation by Sanger dideoxy chain termination sequencing and purify the plasmid using a Qiagen maxiprep kit.

Oligonucleotide synthesis and cells. Chimeric oligonucleotides and single-stranded oligonucleotides (including those with the indicated modifications) are synthesized using available phosphoramidites on controlled pore glass supports. After deprotection and detachment from the solid support, each oligonucleotide is gel-purified using, for example, procedures such as those described in Gamper *et al., Biochem.* 39, 5808-5816 (2000) and the concentrations determined spectrophotometrically (33 or 40 µg/ml per A_{260} unit of single-stranded or hairpin oligomer). HUH7 cells are grown in DMEM, 10% FBS, 2mM glutamine, 0.5% pen/strep. The *E.coli* strain, DH10B, is obtained from Life Technologies (Gaithersburg, MD); DH10B cells contain a mutation in the RECA gene (*rec*A).

Cell-free extracts. We prepare cell-free extracts from HUH7 cells or other mammalian cells, as follows. We employ this protocol with essentially any mammalian cell including, for example, H1299 cells (human epithelial carcinoma, non-small cell lung cancer), C127I (immortal murine mammary epithelial cells), MEF (mouse embryonic fibroblasts), HEC-1-A (human uterine carcinoma), HCT15 (human colon cancer), HCT116 (human colon carcinoma), LoVo (human colon adenocarcinoma), and HeLa (human cervical carcinoma). We harvest approximately $2x10^8$ cells. We then wash the cells immediately in cold hypotonic buffer (20 mM HEPES, pH7.5; 5 mM KCl; 1.5 mM $MgCl_2$; 1 mM DTT) with 250 mM sucrose. We then resuspend the cells in cold hypotonic buffer without sucrose and after 15 minutes we lyse the cells with 25 strokes of a Dounce homogenizer using a tight fitting pestle. We incubate the lysed cells for 60 minutes on ice and centrifuge the sample for 15 minutes at 12000x*g*. The cytoplasmic fraction is enriched with nuclear proteins due to the extended co-incubation of the fractions following cell breakage. We then immediately aliquote and freeze the supernatant at -80°C. We determine the protein concentration in the extract by the Bradford assay.

We also perform these experiments with cell-free extracts obtained from fungal cells, including, for example, *S. cerevisiae* (yeast), *Ustilago maydis*, and *Candida albicans*. For example, we grow yeast cells into log phase in 2L YPD medium for 3 days at 30°C. We then centrifuge the cultures at 5000x*g*, resuspend the pellets in a 10% sucrose, 50 mM Tris, 1mM EDTA lysis solution and freeze them on dry ice. After thawing, we add KCl, spermidine and lyticase to final concentrations of 0.25 mM, 5 mM and 0.1 mg/ml, respectively. We incubate the suspension on ice for 60 minutes, add PMSF and Triton X100 to final concentrations of 0.1 mM and 0.1% and continue to incubate on ice for 20 minutes. We centrifuge the lysate at 3000x*g* for 10 minutes to remove larger debris. We then remove the supernatant and clarify it by centrifuging at 30000x*g* for 15 minutes. We then add glycerol to the clarified extract to a

concentration of 10% (v/v) and freeze aliquots at -80°C. We determine the protein concentration of the extract by the Bradford assay.

Reaction mixtures of 50 μl are used, consisting of 10-30 μg protein of cell-free extract, which can be optionally substituted with purified proteins or enriched fractions, about 1.5 μg chimeric double-hairpin oligonucleotide or 0.55 μg single-stranded molecule (3S/25G or 6S/25G, see Figure 1), and 1 μg of plasmid DNA (see Figures 2 and 3) in a reaction buffer of 20 mM Tris, pH 7.4, 15 mM $MgCl_2$, 0.4 mM DTT, and 1.0 mM ATP. Reactions are initiated with extract and incubated at 30°C for 45 min. The reaction is stopped by placing the tubes on ice and then immediately deproteinized by two phenol/chloroform (1:1) extractions. Samples are then ethanol precipitated. The nucleic acid is pelleted at 15,000 r.p.m. at 4°C for 30 min., is washed with 70% ethanol, resuspended in 50 μl H_20, and is stored at -20°C. 5 μl of plasmid from the resuspension (~100 ng) was transfected in 20 μl of DH10B cells by electroporation (400 V, 300 μF, 4 kΩ) in a Cell-Porator apparatus (Life Technologies). After electroporation, cells are transferred to a 14 ml Falcon snap-cap tube with 2 ml SOC and shaken at 37°C for 1 h. Enhancement of final kan colony counts is achieved by then adding 3 ml SOC with 10 μg/ml kanamycin and the cell suspension is shaken for a further 2 h at 37°C. Cells are then spun down at 3750 x g and the pellet is resuspended in 500 μl SOC. 200 μl is added undiluted to each of two kanamycin (50 μg/ml) agar plates and 200 μl of a 10^5 dilution is added to an ampicillin (100 μg/ml) plate. After overnight 37°C incubation, bacterial colonies are counted using an Accucount 1000 (Biologics). Gene conversion effectiveness is measured as the ratio of the average of the kan colonies on both plates per amp colonies multiplied by 10^{-5} to correct for the amp dilution.

The following procedure can also be used. 5 μl of resuspended reaction mixtures (total volume 50 μl) are used to transform 20 μl aliquots of electro-competent ΔH10B bacteria using a Cell-Porator apparatus (Life Technologies). The mixtures are allowed to recover in 1 ml SOC at 37°C for 1 hour at which time 50 μg/ml kanamycin or 12 μg/ml tetracycline is added for an additional 3 hours. Prior to plating, the bacteria are pelleted and resuspended in 200 μ1 of SOC. 100 μl aliquots are plated onto kan or tet agar plates and 100 μl of a 10^{-4} dilution of the cultures are concurrently plated on agar plates containing 100 μg/ml of ampicillin. Plating is performed in triplicate using sterile Pyrex beads. Colony counts are determined by an Accu-count 1000 plate reader (Biologics). Each plate contains 200-500 ampicillin resistant colonies or 0-500 tetracycline or kanamycin resistant colonies. Resistant colonies are selected for plasmid extraction and DNA sequencing using an ABI Prism kit on an ABI 310 capillary sequencer (PE Biosystems).

Chimeric single-stranded oligonucleotides. In Figure 1 the upper strands of chimeric oligonucleotides I and II are separated into pathways resulting in the generation of single-stranded oligonucleotides that contain (Figure 1A) 2'-O-methyl RNA nucleotides or (Figure 1B) phosphorothioate linkages. Fold changes in repair activity for correction of kan^s in the HUH7 cell-free extract are presented in parenthesis. Each single-stranded oligonucleotide is 25 bases in length and contains a G residue mismatched to the complementary sequence of the kan^s gene.

Molecules bearing 3, 6, 8, 10 and 12 phosphorothioate linkages in the terminal regions at each end of a backbone with a total of 24 linkages (25 bases) are tested in the kan^s system. Alternatively, molecules bearing 2, 4, 5, 7, 9 and 11 in the terminal regions at each end are tested. The results of one such experiment, presented in Table 1 and Figure 1B, illustrate an enhancement of correction activity directed by some of these modified structures. In this illustrative example, the most efficient molecules contained 3 or 6 phosphorothioate linkages at each end of the 25-mer; the activities are approximately equal (molecules IX and X with results of 3.09 and 3.7 respectively). A reduction in alteration activity may be observed as the number of modified linkages in the molecule is further increased. Interestingly, a single-strand molecule containing 24 phosphorothioate linkages is minimally active suggesting that this backbone modification when used throughout the molecule supports only a low level of targeted gene repair or alteration. Such a non-altering, completely modified molecule can provide a baseline control for determining efficiency of correction for a specific oligonucleotide molecule of known sequence in defining the optimum oligonucleotide for a particular alteration event.

The efficiency of gene repair directed by phosphorothioate-modified, single-stranded molecules, in a length dependent fashion, led us to examine the length of the RNA modification used in the original chimera as it relates to correction. Construct III represents the "RNA-containing" strand of chimera I and, as shown in Table 1 and Figure 2A, it promotes inefficient gene repair. But, as shown in the same figure, reducing the RNA residues on each end from 10 to 3 increases the frequency of repair. At equal levels of modification, however, 25-mers with 2'-O-methyl ribonucleotides were less effective gene repair agents than the same oligomers with phosphorothioate linkages. These results reinforce the fact that an RNA containing oligonucleotide is not as effective in promoting gene repair or alteration as a modified DNA oligonucleotide.

Repair of the kanamycin mutation requires a G→C exchange. To confirm that the specific desired correction alteration was obtained, colonies selected at random from multiple experiments are processed and the isolated plasmid DNA is sequenced. As seen in Figure 4, colonies generated through the action of the single-stranded molecules 3S/25G (IX), 6S/25G (X) and 8S/25G (XI) respectively

contained plasmid molecules harboring the targeted base correction. While a few colonies appeared on plates derived from reaction mixtures containing 25-mers with 10 or 12 thioate linkages on both ends, the sequences of the plasmid molecules from these colonies contain nonspecific base changes. In these illustrative examples, the second base of the codon is changed (see Figure 3). These results show that modified single-strands can direct gene repair, but that efficiency and specificity are reduced when the 25-mers contain 10 or more phosphorothioate linkages at each end.

In Figure 1, the numbers 3, 6, 8, 10, 12 and 12.5 respectively indicate how many phosphorothioate linkages (S) or 2'-O-methyl RNA nucleotides (R) are at each end of the examplified molecule although other molecules with 2, 4, 5, 7, 9 and 11 modifications at each end can also be tested. Hence oligo 12S/25G represents a 25-mer oligonucleotide which contains 12 phosphorothioate linkages on each side of the central G target mismatch base producing a fully phosphorothioate linked backbone, displayed as a dotted line. The dots are merely representative of a linkage in the figure and do not depict the actual number of linkages of the oligonucleotide. Smooth lines indicate DNA residues, wavy lines indicate 2'-O-methyl RNA residues and the carat indicates the mismatched base site (G).

Correction of a mutant kanamycin gene in cultured mammalian cells. The experiments are performed using different mammalian cells, including, for example, 293 cells (transformed human primary kidney cells), HeLa cells (human cervical carcinoma), and H1299 (human epithelial carcinoma, non-small cell lung cancer). HeLa cells are grown at 37°C and 5% CO_2 in a humidified incubator to a density of 2 x 10^5 cells/ml in an 8 chamber slide (Lab-Tek). After replacing the regular DMEM with Optimem, the cells are co-transfected with 10 µg of plasmid pAURNeo(-)FlAsH and 5 µg of modified single-stranded oligonucleotide (3S/25G) that is previously complexed with 10 µg lipofectamine, according to the manufacturer's directions (Life Technologies). The cells are treated with the liposome-DNA-oligo mix for 6 hrs at 37°C. Treated cells are washed with PBS and fresh DMEM is added. After a 16-18 hr recovery period, the culture is assayed for gene repair. The same oligonucleotide used in the cell-free extract experiments is used to target transfected plasmid bearing the kan^s gene. Correction of the point mutation in this gene eliminates a stop codon and restores full expression. This expression can be detected by adding a small non-fluorescent ligand that bound to a C-C-R-E-C-C sequence in the genetically modified carboxy terminus of the kan protein, to produce a highly fluorescent complex (FlAsH system, Aurora Biosciences Corporation). Following a 60 min incubation at room temperature with the ligand (FlAsH-EDT2), cells expressing full length kan product acquire an intense green fluorescence detectable by fluorescence microscopy using a fluorescein filter set. Similar experiments are performed using the HygeGFP target as described in Example 2 with a variety of mammalian cells, including, for

example, COS-1 and COS-7 cells (African green monkey), and CHO-K1 cells (Chinese hamster ovary). The experiments are also performed with PG12 cells (rat pheochromocytoma) and ES cells (human embryonic stem cells).

Summary of experimental results. Tables 1, 2 and 3 respectively provide data on the efficiency of gene repair directed by single-stranded oligonucleotides. Table 1 presents data using a cell-free extract from human liver cells (HUH7) to catalyze repair of the point mutation in plasmid pkan^{s}m4021 (see Figure 1). Table 2 illustrates that the oligomers are not dependent on MSH2 or MSH3 for optimal gene repair activity. Table 3 illustrates data from the repair of a frameshift mutation (Figure 3) in the tet gene contained in plasmid pTetΔ208. Table 4 illustrates data from repair of the pkan^{s}m4021 point mutation catalyzed by plant cell extracts prepared from canola and musa (banana). Colony numbers are presented as kan^r or tet^r and fold increases (single strand versus double hairpin) are presented for kan^r in Table 1.

Figure 5A is a confocal picture of HeLa cells expressing the corrected fusion protein from an episomal target. Gene repair is accomplished by the action of a modified single-stranded oligonucleotide containing 3 phosphorothioate linkages at each end (3S/25G). Figure 5B represents a "Z-series" of HeLa cells bearing the corrected fusion gene. This series sections the cells from bottom to top and illustrates that the fluorescent signal is "inside the cells".

Results. In summary, we have designed a novel class of single-stranded oligonucleotides with backbone modifications at the termini and demonstrate gene repair/conversion activity in mammalian and plant cell-free extracts. We confirm that the all DNA strand of the RNA-DNA double-stranded double hairpin chimera is the active component in the process of gene repair. In some cases, the relative frequency of repair by the novel oligonucleotides of the invention is elevated approximately 3-4-fold when compared to frequencies directed by chimeric RNA-DNA double hairpin oligonucleotides.

This strategy centers around the use of extracts from various sources to correct a mutation in a plasmid using a modified single-stranded or a chimeric RNA-DNA double hairpin oligonucleotide. A mutation is placed inside the coding region of a gene conferring antibiotic resistance in bacteria, here kanamycin or tetracycline. The appearance of resistance is measured by genetic readout in *E.coli* grown in the presence of the specified antibiotic. The importance of this system is that both phenotypic alteration and genetic inheritance can be measured. Plasmid pK^{s}m4021 contains a mutation (T→G) at residue 4021 rendering it unable to confer antibiotic resistance in *E.coli.* This point mutation is targeted for repair by oligonucleotides designed to restore kanamycin resistance. To avoid concerns of

plasmid contamination skewing the colony counts, the directed correction is from G→C rather than G→T (wild-type). After isolation, the plasmid is electroporated into the DH10B strain of *E.coli*, which contains inactive RecA protein. The number of kanamycin colonies is counted and normalized by ascertaining the number of ampicillin colonies, a process that controls for the influence of electroporation. The number of colonies generated from three to five independent reactions was averaged and is presented for each experiment. A fold increase number is recorded to aid in comparison.

The original RNA-DNA double hairpin chimera design, e.g., as disclosed in U.S. Patent 5,565,350, consists of two hybridized regions of a single-stranded oligonucleotide folded into a double hairpin configuration. The double-stranded targeting region is made up of a 5 base pair DNA/DNA segment bracketed by 10 base pair RNA/DNA segments. The central base pair is mismatched to the corresponding base pair in the target gene. When a molecule of this design is used to correct the kan^s mutation, gene repair is observed (I in Figure 1A). Chimera II (Figure 1B) differs partly from chimera I in that only the DNA strand of the double hairpin is mismatched to the target sequence. When this chimera was used to correct the kan^s mutation, it was twice as active. In the same study, repair function could be further increased by making the targeting region of the chimera a continuous RNA/DNA hybrid.

Frame shift mutations are repaired. By using plasmid $pT^s\Delta208$, described in Figure 1(C) and Figure 3, the capacity of the modified single-stranded molecules that showed activity in correcting a point mutation, can be tested for repair of a frameshift. To determine efficiency of correction of the mutation, a chimeric oligonucleotide (Tet I), which is designed to insert a T residue at position 208, is used. A modified single-stranded oligonucleotide (Tet IX) directs the insertion of a T residue at this same site. Figure 3 illustrates the plasmid and target bases designated for change in the experiments. When all reaction components are present (extract, plasmid, oligomer), tetracycline resistant colonies appear. The colony count increases with the amount of oligonucleotide used up to a point beyond which the count falls off (Table 3). No colonies above background are observed in the absence of either extract or oligonucleotide, nor when a modified single-stranded molecule bearing perfect complementarity is used. Figure 3 represents the sequence surrounding the target site and shows that a T residue is inserted at the correct site. We have isolated plasmids from fifteen colonies obtained in three independent experiments and each analyzed sequence revealed the same precise nucleotide insertion. These data suggest that the single-stranded molecules used initially for point mutation correction can also repair nucleotide deletions.

Comparison of phosphorothioate oligonucleotides to 2'-O-methyl substituted oligonucleotides. From a comparison of molecules VII and XI, it is apparent that gene repair is more

subject to inhibition by RNA residues than by phosphorothioate linkages. Thus, even though both of these oligonucleotides contain an equal number of modifications to impart nuclease resistance, XI (with 16 phosphorothioate linkages) has good gene repair activity while VII (with 16 2'-O-methyl RNA residues) is inactive. Hence, the original chimeric double hairpin oligonucleotide enabled correction directed, in large part, by the strand containing a large region of contiguous DNA residues.

Oligonucleotides can target multiple nucleotide alterations within the same template. The ability of individual single-stranded oligonucleotides to correct multiple mutations in a single target template is tested using the plasmid pK^{s}m4021 and the following single-stranded oligonucleotides modified with 3 phosphorothioate linkages at each end (indicated as underlined nucleotides): Oligo1 is a 25-mer with the sequence <u>TTC</u>GATAAGCC**T**AT**G**CTGACCC<u>GTG</u> corrects the original mutation present in the kanamycin resistance gene of pK^{s}m4021 as well as directing another alteration 2 basepairs away in the target sequence (both indicated in boldface); Oligo2 is a 70-mer with the 5'-end sequence <u>TTC</u>GGCTA**C**GACTGGGCACAACAGACAAT**T**GGC with the remaining nucleotides being completely complementary to the kanamycin resistance gene and also ending in 3 phosphorothioate linkages at the 3' end. Oligo2 directs correction of the mutation in pK^{s}m4021 as well as directing another alteration 21 basepairs away in the target sequence (both indicated in boldface).

We also use additional oligonucleotides to assay the ability of individual oligonucleotides to correct multiple mutations in the pK^{s}M4021 plasmid. These include, for example, a second 25-mer that alters two nucleotides that are three nucleotides apart with the sequence 5'-TTGTGCCCAGTC<u>**G**</u>TA<u>**T**</u>CCGAATAGC-3'; a 70-mer that alters two nucleotides that are 21 nucleotides apart with the sequence 5'-CATCAGAGCAGCC<u>**A**</u>ATTGTCTGTTGTGCCCAGTC<u>**G**</u>TAGCCGAA TAGCCTCTCCACCCAAGCGGCCGGAGA-3'; and another 70-mer that alters two nucleotides that are 21 nucleotides apart with the sequence 5'-GCTGACAGCCGGAACACGGCGGCATCAGAGCAGCC<u>**A**</u>ATTGTCTGTTGTGCCCAGTC<u>**G**</u>TAGCCGAAT AGCCT-3'. The nucleotides in the oligonucleotides that direct alteration of the target sequence are underlined and in boldface. These oligonucleotides are modified in the same way as the other oligonucleotides of the invention.

We assay correction of the original mutation in pK^{s}m4021 by monitoring kanamycin resistance (the second alterations which are directed by Oligo2 and Oligo3 are silent with respect to the kanamycin resistance phenotype). In addition, in experiments with Oligo2, we also monitor cleavage of the resulting plasmids using the restriction enzyme Tsp509I which cuts at a specific site present only when the second alteration has occurred (at AT**T** in Oligo2). We then sequence these clones to

determine whether the additional, silent alteration has also been introduced. The results of an analysis are presented below:

	Oligo1 (25-mer)	Oligo2 (70-mer)
Clones with both sites changed	9	7
Clones with a single site changed	0	2
Clones that were not changed	4	1

Nuclease sensitivity of unmodified DNA oligonucleotide. Electrophoretic analysis of nucleic acid recovered from the cell-free extract reactions conducted here confirm that the unmodified single-stranded 25-mer did not survive incubation whereas greater than 90% of the terminally modified oligos did survive (as judged by photo-image analyses of agarose gels).

Plant extracts direct repair. The modified single-stranded constructs can be tested in plant cell extracts. We have observed gene alteration using extracts from multiple plant sources, including, for example, Arabidopsis, tobacco, banana, maize, soybean, canola, wheat, spinach as well as spinach chloroplast extract. We prepare the extracts by grinding plant tissue or cultured cells under liquid nitrogen with a mortar and pestle. We extract 3 ml of the ground plant tissue with 1.5 ml of extraction buffer (20 mM HEPES, pH7.5; 5 mM Kcl; 1.5 mM $MgCl_2$; 10 mM DTT; 10% [v/v] glycerol; and 1 % [w/v] PVP). We then homogenize the samples with 15 strokes of a Dounce homogenizer. Following homogenization, we incubate the samples on ice for 1 hour and centrifuge at 3000x*g* for 5 minutes to remove plant cell debris. We then determine the protein concentration in the supernatants (extracts) by Bradford assay. We dispense 100 µg (protein) aliquots of the extracts which we freeze in a dry ice-ethanol bath and store at -80°C.

We describe experiments using two sources here: a dicot (canola) and a monocot (banana, *Musa acuminata* cv. Rasthali). Each vector directs gene repair of the kanamycin mutation (Table 4); however, the level of correction is elevated 2-3 fold relative to the frequency observed with the chimeric oligonucleotide. These results are similar to those observed in the mammalian system wherein a significant improvement in gene repair occurred when modified single-stranded molecules were used.

Tables are attached hereto.

Table I

Gene repair activity is directed by single-stranded oligonucleotides.

Oligonucleotide	Plasmid	Extract (ug)	kan^r colonies	Fold increase
I	pK^{S}m4021	10	300	
I		20	418	1.0x
II		10	537	
II		20	748	1.78x
III		10	3	
III		20	5	0.01x
IV		10	112	
IV		20	96	0.22x
V		10	217	
V		20	342	0.81x
VI		10	6	
VI		20	39	0.093x
VII		10	0	
VII		20	0	0x
VIII		10	3	
VIII		20	5	0.01x
IX		10	936	
IX		20	1295	3.09x
X		10	1140	
X		20	1588	3.7x
XI		10	480	
XI		20	681	1.6x
XII		10	18	
XII		20	25	0.059x
XIII		10	0	
XIII		20	4	0.009x
-		20	0	
I		-	0	

Plasmid pK^{s}m4021 (1 μg), the indicated oligonucleotide (1.5 μg chimeric oligonucleotide or 0.55 μg single-stranded oligonucleotide; molar ratio of oligo to plasmid of 360 to 1) and either 10 or 20 μg of HUH7 cell-free extract were incubated 45 min at 37°C. Isolated plasmid DNA was electroporated into *E. coli* (strain DH10B) and the number of kan^r colonies counted. The data represent the number of kanamycin resistant colonies per 10^6 ampicillin resistant colonies generated from the same reaction and is the average of three

experiments (standard deviation usually less than +/- 15%). Fold increase is defined relative to 418 kan^r colonies (second reaction) and in all reactions was calculated using the 20μg sample.

Table II

Modified single-stranded oligomers are not dependent on MSH2 or MSH3 for optimal gene repair activity.

A.

Oligonucleotide	Plasmid	Extract	kan^r colonies
IX (3S/25G)		HUH7	637
X (6S/25G)		HUH7	836
IX		$MEF2^{-/-}$	781
X		$MEF2^{-/-}$	676
IX		$MEF3^{-/-}$	582
X		$MEF3^{-/-}$	530
IX		$MEF^{+/+}$	332
X		$MEF^{+/+}$	497
-		$MEF2^{-/-}$	10
-		$MEF3^{-/-}$	5
-		$MEF^{+/+}$	14

Chimeric oligonucleotide (1.5 μg) or modified single-stranded oligonucleotide (0.55 μg) was incubated with 1μg of plasmid pK^sm4021 and 20μg of the indicated extracts. MEF represents mouse embryonic fibroblasts with either MSH2 ($2^{-/-}$) or MSH3 ($3^{-/-}$) deleted. $MEF^{+/+}$ indicates wild-type mouse embryonic fibroblasts. The other reaction components were then added and processed through the bacterial readout system. The data represent the number of kanamycin resistant colonies per 10^6 ampicillin resistant colonies.

Table III

Frameshift mutation repair is directed by single-stranded oligonucleotides

Oligonucleotide	Plasmid	Extract	tet^r colonies
Tet IX (3S/25A; 0.5 µg)	$pT^s\Delta208$ (1µg)	-	0
-		20µg	0
Tet IX (0.5 µg)			48
Tet IX (1.5 µg)			130
Tet IX (2.0 µg)			68
Tet I (chimera; 1.5 µg)			48

Each reaction mixture contained the indicated amounts of plasmid and oligonucleotide. The extract used for these experiments came from HUH7 cells. The data represent the number of tetracycline resistant colonies per 10^6 ampicillin resistant colonies generated from the same reaction and is the average of 3 independent experiments. Tet I is a chimeric oligonucleotide and Tet IX is a modified single-stranded oligonucleotide that are designed to insert a T residue at position 208 of $pT^s\Delta208$. These oligonucleotides are equivalent to structures I and IX in Figure 2.

Table IV

Plant cell-free extracts support gene repair by single-stranded oligonucleotides

Oligonucleotide	Plasmid	Extract	kan^r colonies
II (chimera)	pK^Sm4021	30μg Canola	337
IX (3S/25G)		Canola	763
X (6S/25G)		Canola	882
II		*Musa*	203
IX		*Musa*	343
X		*Musa*	746
-		Canola	0
-		*Musa*	0
IX		- Canola	0
X		- *Musa*	0

Canola or Musa cell-free extracts were tested for gene repair activity on the kanamycin-sensitive gene as previously described in (18). Chimeric oligonucleotide II (1.5 μg) and modified single-stranded oligonucleotides IX and X (0.55μg) were used to correct pK^Sm4021. Total number of kan^r colonies are present per 10^7 ampicillin resistant colonies and represent an average of four independent experiments.

Table V

Gene repair activity in cell-free extracts prepared from yeast (Saccharomyces cerevisiae)

Cell-type	Plasmid	Chimeric Oligo	SS Oligo	$kan^r/amp^r \times 10^6$
Wild type	$pKan^s m4021$	1μg		0.36
Wild type			1μg	0.81
ΔRAD52		1μg		10.72
ΔRAD52			1μg	17.41
ΔPMS1		1μg		2.02
ΔPMS1			1μg	3.23

In this experiment, the kan^s gene in $pKan^s 4021$ is corrected by either a chimeric double-hairpin oligonucleotide or a single-stranded oligonucleotide containing three thioate linkages at each end (3S/25G).

EXAMPLE 2
Yeast Cell Targeting Assay Method for Base Alteration and Preferred Oligonucleotide Selection

In this example, single-stranded oligonucleotides with modified backbones and double-hairpin oligonucleotides with chimeric, RNA-DNA backbones are used to measure gene repair using two episomal targets with a fusion between a hygromycin resistance gene and eGFP as a target for gene repair. These plasmids are pAURHYG(rep)GFP, which contains a point mutation in the hygromycin resistance gene (Figure 7), pAURHYG(ins)GFP, which contains a single-base insertion in the hygromycin resistance gene (Figure 7) and pAURHYG(Δ)GFP which has a single base deletion. We also use the plasmid containing a wild-type copy of the hygromycin-eGFP fusion gene, designated pAURHYG(wt)GFP, as a control. These plasmids also contain an aureobasidinA resistance gene. In pAURHYG(rep)GFP, hygromycin resistance gene function and green fluorescence from the eGFP protein are restored when a G at position 137, at codon 46 of the hygromycin B coding sequence, is converted to a C thus removing a premature stop codon in the hygromycin resistance gene coding region. In pAURHYG(ins)GFP, hygromycin resistance gene function and green fluorescence from the eGFP protein are restored when an A inserted between nucleotide positions 136 and 137, at codon 46 of the hygromycin B coding sequence, is deleted and a C is substituted for the T at position 137, thus correcting a frameshift mutation and restoring the reading frame of the hygromycin-eGFP fusion gene.

We synthesize the set of three yeast expression constructs pAURHYG(rep)eGFP, pAURHYG(Δ)eGFP, pAURHYG(ins)eGFP, that contain a point mutation at nucleotide 137 of the hygromycin-B coding sequence as follows. (rep) indicates a T137→G replacement, (Δ) represents a deletion of the G137 and (ins) represents an A insertion between nucleotides 136 and 137. We construct this set of plasmids by excising the respective expression cassettes by restriction digest from pHyg(x)EGFP and ligation into pAUR123 (Panvera, CA). We digest 10 µg pAUR123 vector DNA, as well as, 10 µg of each pHyg(x)EGFP construct with KpnI and SalI (NEB). We gel purify each of the DNA fragments and prepare them for enzymatic ligation. We ligate each mutated insert into pHygEGFP vector at 3:1 molar ration using T4 DNA ligase (Roche). We screen clones by restriction digest, confirm by Sanger dideoxy chain termination sequencing and purify using a Qiagen maxiprep kit.

We use this system to assay the ability of five oligonucleotides (shown in Figure 8) to support correction under a variety of conditions. The oligonucleotides which direct correction of the mutation in pAURHYG(rep)GFP can also direct correction of the mutation in pAURHYG(ins)GFP. Three of the four oligonucleotides (HygE3T/25, HygE3T/74 and HygGG/Rev) share the same 25-base sequence surrounding the base targeted for alteration. HygGG/Rev is an RNA-DNA chimeric double hairpin

oligonucleotide of the type described in the prior art. One of these oligonucleotides, HygE3T/74, is a 74-base oligonucleotide with the 25-base sequence centrally positioned. The fourth oligonucleotide, designated HygE3T/74α, is the reverse complement of HygE3T/74. The fifth oligonucleotide, designated Kan70T, is a non-specific, control oligonucleotide which is not complementary to the target sequence. Alternatively, an oligonucleotide of identical sequence but lacking a mismatch to the target or a completely thioate modified oligonucleotide or a completely 2-0-methylated modified oligonucleotide may be used as a control.

Oligonucleotide synthesis and cells. We synthesized and purified the chimeric, double-hairpin oligonucleotides and single-stranded oligonucleotides (including those with the indicated modifications) as described in Example 1. Plasmids used for assay were maintained stably in yeast (*Saccharomyces cerevisiae*) strain LSY678 *MATα* at low copy number under aureobasidin selection. Plasmids and oligonucleotides are introduced into yeast cells by electroporation as follows: to prepare electrocompetent yeast cells, we inoculate 10 ml of YPD media from a single colony and grow the cultures overnight with shaking at 300 rpm at 30°C. We then add 30 ml of fresh YPD media to the overnight cultures and continue shaking at 30°C until the OD_{600} was between 0.5 and 1.0 (3-5 hours). We then wash the cells by centrifuging at 4°C at 3000 rpm for 5 minutes and twice resuspending the cells in 25 ml ice-cold distilled water. We then centrifuge at 4°C at 3000 rpm for 5 minutes and resuspend in 1 ml ice-cold 1M sorbitol and then finally centrifuge the cells at 4°C at 5000 rpm for 5 minutes and resuspend the cells in 120 µl 1M sorbitol. To transform electrocompetent cells with plasmids or oligonucleotides, we mix 40 µl of cells with 5 µg of nucleic acid, unless otherwise stated, and incubate on ice for 5 minutes. We then transfer the mixture to a 0.2 cm electroporation cuvette and electroporate with a BIO-RAD Gene Pulser apparatus at 1.5 kV, 25 µF, 200 Ω for one five-second pulse. We then immediately resuspend the cells in 1 ml YPD supplemented with 1M sorbitol and incubate the cultures at 30°C with shaking at 300 rpm for 6 hours. We then spread 200 µl of this culture on selective plates containing 300 µg/ml hygromycin and spread 200 µl of a 10^5 dilution of this culture on selective plates containing 500 ng/ml aureobasidinA and/or and incubate at 30°C for 3 days to allow individual yeast colonies to grow. We then count the colonies on the plates and calculate the gene conversion efficiency by determining the number of hygromycin resistance colonies per 10^5 aureobasidinA resistant colonies.

Frameshift mutations are repaired in yeast cells. We test the ability of the oligonucleotides shown in Figure 8 to correct a frameshift mutation *in vivo* using LSY678 yeast cells containing the plasmid pAURHYG(ins)GFP. These experiments, presented in Table 6, indicate that these oligonucleotides can support gene correction in yeast cells. These data reinforce the results described in

Example 1 indicating that oligonucleotides comprising phosphorothioate linkages facilitate gene correction much more efficiently than control duplex, chimeric RNA-DNA oligonucleotides. This gene correction activity is also specific as transformation of cells with the control oligonucleotide Kan70T produced no hygromycin resistant colonies above background and thus Kan70T did not support gene correction in this system. In addition, we observe that the 74-base oligonucleotide (HygE3T/74) corrects the mutation in pAURHYG(ins)GFP approximately five-fold more efficiently than the 25-base oligonucleotide (HygE3T/25). We also perform control experiments with LSY678 yeast cells containing the plasmid pAURHYG(wt)GFP. With this strain we observed that even without added oligonucleotides, there are too many hygromycin resistant colonies to count.

We also use additional oligonucleotides to assay the ability of individual oligonucleotides to correct multiple mutations in the pAURHYG(x)eGFP plasmid. These include, for example, one that alters two basepairs that are 3 nucleotides apart is a 74-mer with the sequence 5'-CTCGTGCTTTCAGCTTCGATGTAGGAGGGCGTGG**G**TA**C**GTCCTGCGGGTAAATAGCTGCGCCGATGGTTTCTAC-3'; a 74-mer that alters two basepairs that are 15 nucleotides apart with the sequence 5'-CTCGTGCTTTCAGCTTCGATGTAGGAGGGCGTGGATA**C**GTCCTGCGGGTAAA**C**AGCTGCGCCGATGGTTTCTAC-3'; and a 74-mer that alters two basepairs that are 27 nucleotides apart with the sequence 5'-CTCGTGCTTTCAGCTTCGATGTAGGAGGGCGTGGATA**C**GTCCTGCGGGTAAATAGCTGCGCCGA**C**GGTTTCTAC. The nucleotides in these oligonucleotides that direct alteration of the target sequence are underlined and in boldface. These oligonucleotides are modified in the same ways as the other oligonucleotides of the invention.

Oligonucleotides targeting the sense strand direct gene correction more efficiently. We compare the ability of single-stranded oligonucleotides to target each of the two strands of the target sequence of both pAURHYG(ins)GFP and pAURHYG(rep)GFP. These experiments, presented in Tables 7 and 8, indicate that an oligonucleotide, HygE3T/74α, with sequence complementary to the sense strand (i.e. the strand of the target sequence that is identical to the mRNA) of the target sequence facilitates gene correction approximately ten-fold more efficiently than an oligonucleotide, HygE3T/74, with sequence complementary to the non-transcribed strand which serves as the template for the synthesis of RNA. As indicated in Table 7, this effect was observed over a range of oligonucleotide concentrations from 0-3.6 μg, although we did observe some variability in the difference between the two oligonucleotides (indicated in Table 7 as a fold difference between HygE3T/74α and HygE3T/74). Furthermore, as shown in Table 8, we observe increased efficiency of correction by HygE3T/74α relative to HygE3T/74 regardless of whether the oligonucleotides were used to correct the base substitution

mutation in pAURHYG(rep)GFP or the insertion mutation in pAURHYG(ins)GFP. The data presented in Table 8 further indicate that the single-stranded oligonucleotides correct a base substitution mutation more efficiently than an insertion mutation. However, this last effect was much less pronounced and the oligonucleotides of the invention are clearly able efficiently to correct both types of mutations in yeast cells. In addition, the role of transcription is investigated using plasmids with inducible promoters such as that described in Figure 10.

Optimization of oligonucleotide concentration. To determine the optimal concentration of oligonucleotide for the purpose of gene alteration, we test the ability of increasing concentrations of Hyg3T/74α to correct the mutation in pAURHYG(rep)GFP contained in yeast LSY678. We chose this assay system because our previous experiments indicated that it supports the highest level of correction. However, this same approach could be used to determine the optimal concentration of any given oligonucleotide. We test the ability of Hyg3T/74α to correct the mutation in pAURHYG(rep)GFP contained in yeast LSY678 over a range of oligonucleotide concentrations from 0-10.0 μg. As shown in Table 9, we observe that the correction efficiency initially increases with increasing oligonucleotide concentration, but then declines at the highest concentration tested.

Tables are attached hereto.

Table 6

Correction of an insertion mutation in pAURHYG(ins)GFP by HygGG/Rev, HygE3T/25 and HygE3T/74

Oligonucleotide Tested	Colonies on Hygromycin	Colonies on Aureobasidin (/10^5)	Correction Efficiency
HygGG/Rev	3	157	0.02
HygE3T/25	64	147	0.44
HygE3T/74	280	174	1.61
Kan70T	0	—	—

Table 7

An oligonucleotide targeting the sense strand of the target sequence corrects more efficiently.

Amount of Oligonucleotide (μg)	Colonies per hygromycin plate	
	HygE3T/74	HygE3T/74α
0	0	0
0.6	24	128 (8.4x)*
1.2	69	140 (7.5x)*
2.4	62	167 (3.8x)*
3.6	29	367 (15x)*

* The numbers in parentheses represent the fold increase in efficiency for targeting the non-transcribed strand as compared to the other strand of a DNA duplex that encodes a protein.

Table 8

Correction of a base substitution mutation is more efficient than correction of a frame shift mutation.

Oligonucleotide Tested (5 μg)	Plasmid tested (contained in LSY678)	
	pAURHYG(ins)GFP	pAURHYG(rep)GFP
HygE3T/74	72	277
HygE3T/74α	1464	2248
Kan70T	0	0

Table 9

Optimization of oligonucleotide concentration in electroporated yeast cells.

Amount (μg)	Colonies on hygromycin	Colonies on aureobasidin (/10^5)	Correction efficiency
0	0	67	0
1.0	5	64	0.08
2.5	47	30	1.57
5.0	199	33	6.08
7.5	383	39	9.79
10.0	191	33	5.79

Example 3
Cultured Cell Manipulation

Mononuclear cells are isolated from human umbilical cord blood of normal donors using Ficoll Hypaque (Pharmacia Biotech, Uppsala, Sweden) density centrifugation. CD34+ cells are immunomagnetically purified from mononuclear cells using either the progenitor or Multisort Kits (Miltenyi Biotec, Auburn, CA). $Lin^{-}CD38^{-}$ cells are purified from the mononuclear cells using negative selection with StemSep system according to the manufacturer's protocol (Stem Cell Technologies, Vancouver, CA).

Cells used for microinjection are either freshly isolated or cryopreserved and cultured in Stem Medium (S Medium) for 2 to 5 days prior to microinjection. S Medium contains Iscoves' Modified Dulbecco's Medium without phenol red (IMDM) with 100 μg/ml glutamine/penicillin/streptomycin, 50 mg/ml bovine serum albumin, 50 μg/ml bovine pancreatic insulin, 1 mg/ml human transferrin, and IMDM; Stem Cell Technologies), 40 μg/ml low-density lipoprotein (LDL; Sigma, St. Louis, MO), 50 mM HEPEs buffer and 50 μM 2-mercaptoethanol, 20 ng/ml each of thrombopoietin, flt-3 ligand, stem cell factor and human IL-6 (Pepro Tech Inc., Rocky Hill, NJ). After microinjection, cells are detached and transferred in bulk into wells of 48 well plates for culturing.

35 mm dishes are coated overnight at 4° C with 50 μg/ml Fibronectin (FN) fragment CH-296 (Retronectin; TaKaRa Biomedicals, Panvera, Madison, WI) in phosphate buffered saline and washed with IMDM containing glutamine/penicillin/streptomycin. 300 to 2000 cells are added to cloning rings and attached to the plates for 45 minutes at 37° C prior to microinjection. After incubation, cloning rings are removed and 2 ml of S Medium are added to each dish for microinjection. Pulled injection needles with a range of 0.22 μ to 0.3 μ outer tip diameter are used. Cells are visualized with a microscope equipped with a temperature controlled stage set at 37° C and injected using an electronically interfaced Eppendorf Micromanipulator and Transjector. Successfully injected cells are intact, alive and remain attached to the plate post injection. Molecules that are flourescently labeled allow determination of the amount of oligonucleotide delivered to the cells.

For in vitro erythropoiesis from $Lin^{-}CD38^{-}$ cells, the procedure of Malik, 1998 can be used. Cells are cultured in ME Medium for 4 days and then cultured in E Medium for 3 weeks. Erythropoiesis is evident by glycophorin A expression as well as the presence of red color representing the presence of hemoglobin in the cultured cells. The injected cells are able to retain their proliferative capacity and the ability to generate myeloid and erythoid progeny. CD34+ cells can convert a normal A (β^A) to sickle T (β^S) mutation in the β-globin gene or can be altered using any of the oligonucleotides of the invention herein for correction or alteration of a normal gene to a mutant gene. Alternatively, stem cells can be isolated from blood of humans having genetic disease mutations and the oligonucleotides of the invention can be used to correct a defect or to modify genomes within those cells.

Alternatively, non-stem cell populations of cultured cells can be manipulated using any method known to those of skill in the art including, for example, the use of polycations, cationic lipids, liposomes, polyethylenimine (PEI), electroporation, biolistics, calcium phophate precipitation, or any other method known in the art.

Notes on the tables presented below:

Each of the following tables presents, for the specified human gene, a plurality of mutations that are known to confer a clinically-relevant phenotype and, for each mutation, the oligonucleotides that can be used to correct the respective mutation site-specifically in the human genome according to the present invention.

The left-most column identifies each mutation and the clinical phenotype that the mutation confers.

For most entries, the mutation is identified at both the nucleic acid and protein level. At the amino acid level, mutations are presented according to the following standard nomenclature. The centered number identifies the position of the mutated codon in the protein sequence; to the left of the number is the wild type residue and to the right of the number is the mutant codon. Codon numbering is according to the Human Gene Mutation Database, Cardiff, Wales, UK (http://archive.uwcm.ac.uk/search/mg/allgenes). Terminator codons are shown as "TERM". At the nucleic acid level, the entire triplet of the wild type and mutated codons is shown.

The middle column presents, for each mutation, four oligonucleotides capable of repairing the mutation site-specifically in the human genome or in cloned human DNA including human DNA in artificial chromosomes, episomes, plasmids, or other types of vectors. The oligonucleotides of the invention, however, may include any of the oligonucleotides sharing portions of the sequence of the 121 base sequence. Thus, oligonucleotides of the invention for each of the depicted targets may be 18, 19, 20 up to about 121 nucleotides in length. Sequence may be added non-symmetrically.

All oligonucleotides are presented, per convention, in the 5' to 3' orientation. The nucleotide that effects the change in the genome is underlined and presented in bold.

The first of the four oligonucleotides for each mutation is a 121 nt oligonucleotide centered about the repair nucleotide. The second oligonucleotide, its reverse complement, targets the opposite strand of the DNA duplex for repair. The third oligonucleotide is the minimal 17 nt domain of the first oligonucleotide, also centered about the repair nucleotide. The fourth oligonucleotide is the reverse complement of the third, and thus represents the minimal 17 nt domain of the second.

The third column of each table presents the SEQ ID NO: of the respective repair oligonucleotide.

EXAMPLE 4
Adenosine Deaminase (ADA)

Adenosine deaminase (ADA, EC 3.5.4.4) catalyses the deamination of adenosine and 2'-deoxyadenosine to inosine or 2'-deoxyinosine respectively. ADA deficiency has been identified as the metabolic basis for 20-30% of cases with recessively inherited severe combined immunodeficiency (SCID). Affected infants are subject to recurrent chronic viral, fungal, protozoal, and bacterial infections and frequently present with persistent diarrhea, failure to thrive and candidiasis. In patients homozygous for ADA deficiency, 2'-deoxyadenosine accumulating during the rapid turnover of cells rich in DNA is converted back to dATP, either by adenosine kinase or deoxycytidine kinase. Many hypotheses have been advanced to explain the specific toxicity to the immune system in ADA deficiency. The apparently selective accumulation of dATP in thymocytes and peripheral blood B cells, with resultant inhibition of ribonucleotide reductase and DNA synthesis is probably the principal mechanism.

The structural gene for ADA is encoded as a single 32 kb locus containing 12 exons. Studies of the molecular defect in ADA-deficient patients have shown that mRNA is usually detectable in normal or supranormal amounts. Specific base substitution mutations have been detected in the majority of cases with the complete deficiency. A C-to-T base substitution mutation in exon 11 accounts for a high proportion of these, whilst a few patients are homozygous for large deletions encompassing exon I. A common point mutation resulting in a heat-labile ADA has been characterised in some patients with partial ADA deficiency, a disorder with an apparently increased prevalence in the Caribbean.

As yet no totally effective therapy for ADA deficiency has been reported, except in those few cases where bone marrow from an HLA/MLR compatible sibling donor was available.

Two therapeutic approaches have provided long-term benefit in specific instances. First, reconstitution using T cell depleted mismatched sibling marrow has been encouraging, particularly in early presenters completely deficient in ADA. Secondly, therapy with polyethylene glycol-modified adenosine deaminase (PEG-ADA) for more than 5 years has produced a sustained increase in lymphocyte numbers and mitogen responses together with evidence of in vivo B cell function. Success has generally been achieved in late presenters with residual ADA activity in mononuclear cells.

ADA deficiency has been chosen as the candidate disease for gene replacement therapy and the first human experiment commenced in 1990. The clinical consequences of overexpression of ADA activity - one of the potential hazards of gene implant - are known and take the form of an hereditary haemolytic anaemia associated with a tissue-specific increase in ADA activity. The genetic basis for the

latter autosomal dominant disorder seemingly relates to markedly increased levels of structurally normal ADA mRNA.

Table 10
ADA Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency GLN3TERM CAG to TAG	AGAGACCCACCGAGCGGCGGCGGAGGGAGCAGCGCCGGGG CGCACGAGGGCACCATGGCC**C**AGACGCCCGCCTTCGACAAG CCCAAAGTGAGCGCGCGCGGGGGCTCCGGGGACGGGGTC	1
	GACCCCCGTCCCCGGAGCCCCCGCGCGCGCTCACTTTGGG CTTGTCGAAGGCGGGCGTCT**G**GGCCATGGTGCCCTCGTGCG CCCCGGCGCTGCTCCCTCCGCCGCCGCTCGGTGGGTCTCT	2
	CCATGGCC**C**AGACGCCC	3
	GGGCGTCT**G**GGCCATGG	4
Adenosine deaminase deficiency HIS15ASP CAT to GAT	TATTTGTTCTCTCTCTCCCTTTCTCTCTCTCTTCCCCCTGCCC CCTTGCAGGTAGAACTG**C**ATGTCCACCTAGACGGATCCATCA AGCCTGAAACCATCTTATACTATGGCAGGTAAGTCC	5
	GGACTTACCTGCCATAGTATAAGATGGTTTCAGGCTTGATGGA TCCGTCTAGGTGGACAT**G**CAGTTCTACCTGCAAGGGGGCAG GGGGAAGAGAGAGAGAAAGGGAGAGAGAGAACAAATA	6
	TAGAACTG**C**ATGTCCAC	7
	GTGGACAT**G**CAGTTCTA	8
Adenosine deaminase deficiency GLY20ARG GGA to AGA	TCCCTTTCTCTCTCTCTTCCCCCTGCCCCCTTGCAGGTAGAA CTGCATGTCCACCTAGAC**G**GATCCATCAAGCCTGAAACCATC TTATACTATGGCAGGTAAGTCCATACAGAAGAGCCCT	9
	AGGGCTCTTCTGTATGGACTTACCTGCCATAGTATAAGATGGT TTCAGGCTTGATGGATC**C**GTCTAGGTGGACATGCAGTTCTAC CTGCAAGGGGGCAGGGGGAAGAGAGAGAGAAAGGGA	10
	ACCTAGAC**G**GATCCATC	11
	GATGGATC**C**GTCTAGGT	12
Adenosine deaminase deficiency GLY74CYS GGC to TGC	CCTGGAGCTCCCAAGGGACTTGGGGAAGGTTGTTCCCAACC CCTTTCTTCCCTTCCCAGG**G**GCTGCCGGGAGGCTATCAAAAG GATCGCCTATGAGTTTGTAGAGATGAAGGCCAAAGAGG	13

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CCTCTTTGGCCTTCATCTCTACAAACTCATAGGCGATCCTTTT GATAGCCTCCCGGCAGC**C**CCTGGGAAGGGAAGAAAGGGGTT GGGAACAACCTTCCCCAAGTCCCTTGGGAGCTCCAGG	14
	CTATCGCG**G**GCTGCCGG	15
	CCGGCAGC**C**CGCGATAG	16
Adenosine Deaminase Deficiency ARG76TRP CGG to TGG	GCTCCCAAGGGACTTGGGGAAGGTTGTTCCCAACCCCTTTCT TCCCTTCCCAGGGGCTGC**C**GGGAGGCTATCAAAAGGATCGC CTATGAGTTTGTAGAGATGAAGGCCAAAGAGGGCGTGG	17
	CCACGCCCTCTTTGGCCTTCATCTCTACAAACTCATAGGCGAT CCTTTTGATAGCCTCCC**G**GCAGCCCCTGGGAAGGGAAGAAA GGGGTTGGGAACAACCTTCCCCAAGTCCCTTGGGAGC	18
	GGGGCTGC**C**GGGAGGCT	19
	AGCCTCCC**G**GCAGCCCC	20
Adenosine Deaminase Deficiency LYS80ARG AAA to AGA	TTGGGGAAGGTTGTTCCCAACCCCTTTCTTCCCTTCCCAGGG GCTGCCGGGAGGCTATCA**A**AAGGATCGCCTATGAGTTTGTAG AGATGAAGGCCAAAGAGGGCGTGGTGTATGTGGAGGT	21
	ACCTCCACATACACCACGCCCTCTTTGGCCTTCATCTCTACAA ACTCATAGGCGATCCTT**T**TGATAGCCTCCCGGCAGCCCCTGG GAAGGGAAGAAAGGGGTTGGGAACAACCTTCCCCAA	22
	GGCTATCA**A**AAGGATCG	23
	CGATCCTT**T**TGATAGCC	24
Adenosine deaminase deficiency ALA83ASP GCC to GAC	GTTGTTCCCAACCCCTTTCTTCCCTTCCCAGGGGCTGCCGGG AGGCTATCAAAAGGATCG**C**CTATGAGTTTGTAGAGATGAAGG CCAAAGAGGGCGTGGTGTATGTGGAGGTGCGGTACAG	25
	CTGTACCGCACCTCCACATACACCACGCCCTCTTTGGCCTTC ATCTCTACAAACTCATAG**G**CGATCCTTTTGATAGCCTCCCGGC AGCCCCTGGGAAGGGAAGAAAGGGGTTGGGAACAAC	26
	AAGGATCG**C**CTATGAGT	27
	ACTCATAG**G**CGATCCTT	28
Adenosine deaminase deficiency TYR97CYS TAT to TGT	AGGCTATCAAAAGGATCGCCTATGAGTTTGTAGAGATGAAGG CCAAAGAGGGCGTGGTGT**A**TGTGGAGGTGCGGTACAGTCCG CACCTGCTGGCCAACTCCAAAGTGGAGCCAATCCCCTG	29
	CAGGGGATTGGCTCCACTTTGGAGTTGGCCAGCAGGTGCGG ACTGTACCGCACCTCCACA**T**ACACCACGCCCTCTTTGGCCTT CATCTCTACAAACTCATAGGCGATCCTTTTGATAGCCT	30

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CGTGGTGT**A**TGTGGAGG	31
	CCTCCACA**T**ACACCACG	32
Adenosine deaminase deficiency ARG101GLN CGG to CAG	GGATCGCCTATGAGTTTGTAGAGATGAAGGCCAAAGAGGGCG TGGTGTATGTGGAGGTGC**G**GTACAGTCCGCACCTGCTGGCC AACTCCAAAGTGGAGCCAATCCCCTGGAACCAGGCTGA	33
	TCAGCCTGGTTCCAGGGGATTGGCTCCACTTTGGAGTTGGCC AGCAGGTGCGGACTGTAC**C**GCACCTCCACATACACCACGCC CTCTTTGGCCTTCATCTCTACAAACTCATAGGCGATCC	34
	GGAGGTGC**G**GTACAGTC	35
	GACTGTAC**C**GCACCTCC	36
Adenosine deaminase deficiency ARG101LEU CGG to CTG	GGATCGCCTATGAGTTTGTAGAGATGAAGGCCAAAGAGGGCG TGGTGTATGTGGAGGTGC**G**GTACAGTCCGCACCTGCTGGCC AACTCCAAAGTGGAGCCAATCCCCTGGAACCAGGCTGA	37
	TCAGCCTGGTTCCAGGGGATTGGCTCCACTTTGGAGTTGGCC AGCAGGTGCGGACTGTAC**C**GCACCTCCACATACACCACGCC CTCTTTGGCCTTCATCTCTACAAACTCATAGGCGATCC	38
	GGAGGTGC**G**GTACAGTC	39
	GACTGTAC**C**GCACCTCC	40
Adenosine deaminase deficiency ARG101TRP CGG to TGG	AGGATCGCCTATGAGTTTGTAGAGATGAAGGCCAAAGAGGGC GTGGTGTATGTGGAGGTG**C**GGTACAGTCCGCACCTGCTGGC CAACTCCAAAGTGGAGCCAATCCCCTGGAACCAGGCTG	41
	CAGCCTGGTTCCAGGGGATTGGCTCCACTTTGGAGTTGGCCA GCAGGTGCGGACTGTACC**G**CACCTCCACATACACCACGCCC TCTTTGGCCTTCATCTCTACAAACTCATAGGCGATCCT	42
	TGGAGGTG**C**GGTACAGT	43
	ACTGTACC**G**CACCTCCA	44
Adenosine deaminase deficiency PRO104LEU CCG to CTG	ATGAGTTTGTAGAGATGAAGGCCAAAGAGGGCGTGGTGTATG TGGAGGTGCGGTACAGTC**C**GCACCTGCTGGCCAACTCCAAA GTGGAGCCAATCCCCTGGAACCAGGCTGAGTGAGTGAT	45
	ATCACTCACTCAGCCTGGTTCCAGGGGATTGGCTCCACTTTG GAGTTGGCCAGCAGGTGC**G**GACTGTACCGCACCTCCACATA CACCACGCCCTCTTTGGCCTTCATCTCTACAAACTCAT	46
	GTACAGTC**C**GCACCTGC	47
	GCAGGTGC**G**GACTGTAC	48

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency LEU106VAL CTG to GTG	TTTGTAGAGATGAAGGCCAAAGAGGGCGTGGTGTATGTGGAG GTGCGGTACAGTCCGCAC**C**TGCTGGCCAACTCCAAAGTGGA GCCAATCCCCTGGAACCAGGCTGAGTGAGTGATGGGCC	49
	GGCCCATCACTCACTCAGCCTGGTTCCAGGGGATTGGCTCCA CTTTGGAGTTGGCCAGCA**G**GTGCGGACTGTACCGCACCTCC ACATACACCACGCCCTCTTTGGCCTTCATCTCTACAAA	50
	GTCCGCAC**C**TGCTGGCC	51
	GGCCAGCA**G**GTGCGGAC	52
Adenosine deaminase deficiency LEU107PRO CTG to CCG	TAGAGATGAAGGCCAAAGAGGGCGTGGTGTATGTGGAGGTG CGGTACAGTCCGCACCTGC**T**GGCCAACTCCAAAGTGGAGCC AATCCCCTGGAACCAGGCTGAGTGAGTGATGGGCCTGGA	53
	TCCAGGCCCATCACTCACTCAGCCTGGTTCCAGGGGATTGGC TCCACTTTGGAGTTGGCC**A**GCAGGTGCGGACTGTACCGCAC CTCCACATACACCACGCCCTCTTTGGCCTTCATCTCTA	54
	GCACCTGC**T**GGCCAACT	55
	AGTTGGCC**A**GCAGGTGC	56
Adenosine deaminase deficiency PRO126GLN CCA to CAA	GCCTTCCTTTTGCCTCAGGCCCATCCCTACTCCTCTCCTCAC ACAGAGGGGACCTCACCC**C**AGACGAGGTGGTGGCCCTAGTG GGCCAGGGCCTGCAGGAGGGGGAGCGAGACTTCGGGGT	57
	ACCCCGAAGTCTCGCTCCCCCTCCTGCAGGCCCTGGCCCAC TAGGGCCACCACCTCGTCT**G**GGGTGAGGTCCCCTCTGTGTG AGGAGAGGAGTAGGGATGGGCCTGAGGCAAAAGGAAGGC	58
	CCTCACCC**C**AGACGAGG	59
	CCTCGTCT**G**GGGTGAGG	60
Adenosine deaminase deficiency VAL129MET GTG to ATG	TTTGCCTCAGGCCCATCCCTACTCCTCTCCTCACACAGAGGG GACCTCACCCCAGACGAG**G**TGGTGGCCCTAGTGGGCCAGGG CCTGCAGGAGGGGGAGCGAGACTTCGGGGTCAAGGCCC	61
	GGGCCTTGACCCCGAAGTCTCGCTCCCCCTCCTGCAGGCCC TGGCCCACTAGGGCCACCA**C**CTCGTCTGGGGTGAGGTCCCC TCTGTGTGAGGAGAGGAGTAGGGATGGGCCTGAGGCAAA	62
	CAGACGAG**G**TGGTGGCC	63
	GGCCACCA**C**CTCGTCTG	64

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency GLY140GLU GGG to GAG	ACAGAGGGGACCTCACCCCAGACGAGGTGGTGGCCCTAGTG GGCCAGGGCCTGCAGGAGG**G**GGAGCGAGACTTCGGGGTCA AGGCCCGGTCCATCCTGTGCTGCATGCGCCACCAGCCCAG	65
	CTGGGCTGGTGGCGCATGCAGCACAGGATGGACCGGGCCTT GACCCCGAAGTCTCGCTCC**C**CCTCCTGCAGGCCCTGGCCCA CTAGGGCCACCACCTCGTCTGGGGTGAGGTCCCCTCTGT	66
	GCAGGAGG**G**GGAGCGAG	67
	CTCGCTCC**C**CCTCCTGC	68
Adenosine deaminase deficiency ARG142GLN CGA to CAA	GGGACCTCACCCCAGACGAGGTGGTGGCCCTAGTGGGCCAG GGCCTGCAGGAGGGGGAGC**G**AGACTTCGGGGTCAAGGCCC GGTCCATCCTGTGCTGCATGCGCCACCAGCCCAGTGAGTA	69
	TACTCACTGGGCTGGTGGCGCATGCAGCACAGGATGGACCG GGCCTTGACCCCGAAGTCT**C**GCTCCCCCTCCTGCAGGCCCT GGCCCACTAGGGCCACCACCTCGTCTGGGGTGAGGTCCC	70
	GGGGGAGC**G**AGACTTCG	71
	CGAAGTCT**C**GCTCCCCC	72
Adenosine deaminase deficiency ARG142TERM CGA to TGA	GGGGACCTCACCCCAGACGAGGTGGTGGCCCTAGTGGGCCA GGGCCTGCAGGAGGGGGAG**C**GAGACTTCGGGGTCAAGGCC CGGTCCATCCTGTGCTGCATGCGCCACCAGCCCAGTGAGT	73
	ACTCACTGGGCTGGTGGCGCATGCAGCACAGGATGGACCGG GCCTTGACCCCGAAGTCTC**G**CTCCCCCTCCTGCAGGCCCTG GCCCACTAGGGCCACCACCTCGTCTGGGGTGAGGTCCCC	74
	AGGGGGAG**C**GAGACTTC	75
	GAAGTCTC**G**CTCCCCCT	76
Adenosine deaminase deficiency ARG149GLN CGG to CAG	TGGTGGCCCTAGTGGGCCAGGGCCTGCAGGAGGGGGAGCG AGACTTCGGGGTCAAGGCCC**G**GTCCATCCTGTGCTGCATGC GCCACCAGCCCAGTGAGTAGGATCACCGCCCTGCCCAGGG	77
	CCCTGGGCAGGGCGGTGATCCTACTCACTGGGCTGGTGGCG CATGCAGCACAGGATGGAC**C**GGGCCTTGACCCCGAAGTCTC GCTCCCCCTCCTGCAGGCCCTGGCCCACTAGGGCCACCA	78
	CAAGGCCC**G**GTCCATCC	79
	GGATGGAC**C**GGGCCTTG	80

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency ARG149TRP CGG to TGG	GTGGTGGCCCTAGTGGGCCAGGGCCTGCAGGAGGGGGAGC GAGACTTCGGGGTCAAGGCC**C**GGTCCATCCTGTGCTGCATG CGCCACCAGCCCAGTGAGTAGGATCACCGCCCTGCCCAGG	81
	CCTGGGCAGGGCGGTGATCCTACTCACTGGGCTGGTGGCGC ATGCAGCACAGGATGGACC**G**GGCCTTGACCCCGAAGTCTCG CTCCCCCTCCTGCAGGCCCTGGCCCACTAGGGCCACCAC	82
	TCAAGGCC**C**GGTCCATC	83
	GATGGACC**G**GGCCTTGA	84
Adenosine deaminase deficiency LEU152MET CTG to ATG	CTAGTGGGCCAGGGCCTGCAGGAGGGGGAGCGAGACTTCG GGGTCAAGGCCCGGTCCATC**C**TGTGCTGCATGCGCCACCAG CCCAGTGAGTAGGATCACCGCCCTGCCCAGGGCCGCCCGT	85
	ACGGGCGGCCCTGGGCAGGGCGGTGATCCTACTCACTGGG CTGGTGGCGCATGCAGCACA**G**GATGGACCGGGCCTTGACCC CGAAGTCTCGCTCCCCCTCCTGCAGGCCCTGGCCCACTAG	86
	GGTCCATC**C**TGTGCTGC	87
	GCAGCACA**G**GATGGACC	88
Adenosine deaminase deficiency ARG156CYS CGC to TGC	GGCCTGCAGGAGGGGGAGCGAGACTTCGGGGTCAAGGCCC GGTCCATCCTGTGCTGCATG**C**GCCACCAGCCCAGTGAGTAG GATCACCGCCCTGCCCAGGGCCGCCCGTCTCACCCTGGCC	89
	GGCCAGGGTGAGACGGGCGGCCCTGGGCAGGGCGGTGATC CTACTCACTGGGCTGGTGGC**G**CATGCAGCACAGGATGGACC GGGCCTTGACCCCGAAGTCTCGCTCCCCCTCCTGCAGGCC	90
	GCTGCATG**C**GCCACCAG	91
	CTGGTGGC**G**CATGCAGC	92
Adenosine deaminase deficiency ARG156HIS CGC to CAC	GCCTGCAGGAGGGGGAGCGAGACTTCGGGGTCAAGGCCCG GTCCATCCTGTGCTGCATGC**G**CCACCAGCCCAGTGAGTAGG ATCACCGCCCTGCCCAGGGCCGCCCGTCTCACCCTGGCCC	93
	GGGCCAGGGTGAGACGGGCGGCCCTGGGCAGGGCGGTGAT CCTACTCACTGGGCTGGTGG**C**GCATGCAGCACAGGATGGAC CGGGCCTTGACCCCGAAGTCTCGCTCCCCCTCCTGCAGGC	94
	CTGCATGC**G**CCACCAGC	95
	GCTGGTGG**C**GCATGCAG	96

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency VAL177MET GTG to ATG	CTGCCCACAGACTGGTCCCCCAAGGTGGTGGAGCTGTGTAA GAAGTACCAGCAGCAGACC**G**TGGTAGCCATTGACCTGGCTG GAGATGAGACCATCCCAGGAAGCAGCCTCTTGCCTGGAC	97
	GTCCAGGCAAGAGGCTGCTTCCTGGGATGGTCTCATCTCCAG CCAGGTCAATGGCTACCA**C**GGTCTGCTGCTGGTACTTCTTAC ACAGCTCCACCACCTTGGGGGACCAGTCTGTGGGCAG	98
	AGCAGACC**G**TGGTAGCC	99
	GGCTACCA**C**GGTCTGCT	100
Adenosine deaminase deficiency ALA179ASP GCC to GAC	CAGACTGGTCCCCCAAGGTGGTGGAGCTGTGTAAGAAGTAC CAGCAGCAGACCGTGGTAG**C**CATTGACCTGGCTGGAGATGA GACCATCCCAGGAAGCAGCCTCTTGCCTGGACATGTCCA	101
	TGGACATGTCCAGGCAAGAGGCTGCTTCCTGGGATGGTCTCA TCTCCAGCCAGGTCAATG**G**CTACCACGGTCTGCTGCTGGTAC TTCTTACACAGCTCCACCACCTTGGGGGACCAGTCTG	102
	CGTGGTAG**C**CATTGACC	103
	GGTCAATG**G**CTACCACG	104
Adenosine deaminase deficiency GLN199PRO CAG to CCG	CCATTGACCTGGCTGGAGATGAGACCATCCCAGGAAGCAGC CTCTTGCCTGGACATGTCC**A**GGCCTACCAGGTGGGTCCTGT GAGAAGGAATGGAGAGGCTGGCCCTGGGTGAGCTTGTCT	105
	AGACAAGCTCACCCAGGGCCAGCCTCTCCATTCCTTCTCACA GGACCCACCTGGTAGGCC**T**GGACATGTCCAGGCAAGAGGCT GCTTCCTGGGATGGTCTCATCTCCAGCCAGGTCAATGG	106
	ACATGTCC**A**GGCCTACC	107
	GGTAGGCC**T**GGACATGT	108
Adenosine deaminase deficiency ARG211CYS CGT to TGT	GCTAGGGCACCCATGACCTGGCTCTCCCCCTTCCAGGAGGC TGTGAAGAGCGGCATTCAC**C**GTACTGTCCACGCCGGGGAGG TGGGCTCGGCCGAAGTAGTAAAAGAGGTGAGGGCCTGGG	109
	CCCAGGCCCTCACCTCTTTTACTACTTCGGCCGAGCCCACCT CCCCGGCGTGGACAGTAC**G**GTGAATGCCGCTCTTCACAGCC TCCTGGAAGGGGGAGAGCCAGGTCATGGGTGCCCTAGC	110
	GCATTCAC**C**GTACTGTC	111
	GACAGTAC**G**GTGAATGC	112

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency ARG211HIS CGT to CAT	CTAGGGCACCCATGACCTGGCTCTCCCCCTTCCAGGAGGCT GTGAAGAGCGGCATTCACC**G**TACTGTCCACGCCGGGGAGGT GGGCTCGGCCGAAGTAGTAAAAGAGGTGAGGGCCTGGGC	113
	GCCCAGGCCCTCACCTCTTTTACTACTTCGGCCGAGCCCACC TCCCCGGCGTGGACAGTA**C**GGTGAATGCCGCTCTTCACAGC CTCCTGGAAGGGGGAGAGCCAGGTCATGGGTGCCCTAG	114
	CATTCACC**G**TACTGTCC	115
	GGACAGTA**C**GGTGAATG	116
Adenosine deaminase deficiency ALA215THR GCC to ACC	ATGACCTGGCTCTCCCCCTTCCAGGAGGCTGTGAAGAGCGG CATTCACCGTACTGTCCAC**G**CCGGGGAGGTGGGCTCGGCCG AAGTAGTAAAAGAGGTGAGGGCCTGGGCTGGCCATGGGG	117
	CCCCATGGCCAGCCCAGGCCCTCACCTCTTTTACTACTTCGG CCGAGCCCACCTCCCCGG**C**GTGGACAGTACGGTGAATGCCG CTCTTCACAGCCTCCTGGAAGGGGGAGAGCCAGGTCAT	118
	CTGTCCAC**G**CCGGGGAG	119
	CTCCCCGG**C**GTGGACAG	120
Adenosine deaminase deficiency GLY216ARG GGG to AGG	ACCTGGCTCTCCCCCTTCCAGGAGGCTGTGAAGAGCGGCAT TCACCGTACTGTCCACGCC**G**GGGAGGTGGGCTCGGCCGAAG TAGTAAAAGAGGTGAGGGCCTGGGCTGGCCATGGGGTCC	121
	GGACCCCATGGCCAGCCCAGGCCCTCACCTCTTTTACTACTT CGGCCGAGCCCACCTCCC**C**GGCGTGGACAGTACGGTGAATG CCGCTCTTCACAGCCTCCTGGAAGGGGGAGAGCCAGGT	122
	TCCACGCC**G**GGGAGGTG	123
	CACCTCCC**C**GGCGTGGA	124
Adenosine deaminase deficiency GLU217LYS GAG to AAG	TGGCTCTCCCCCTTCCAGGAGGCTGTGAAGAGCGGCATTCA CCGTACTGTCCACGCCGGG**G**AGGTGGGCTCGGCCGAAGTAG TAAAAGAGGTGAGGGCCTGGGCTGGCCATGGGGTCCCTC	125
	GAGGGACCCCATGGCCAGCCCAGGCCCTCACCTCTTTTACTA CTTCGGCCGAGCCCACCT**C**CCCGGCGTGGACAGTACGGTGA ATGCCGCTCTTCACAGCCTCCTGGAAGGGGGAGAGCCA	126
	ACGCCGGG**G**AGGTGGGC	127
	GCCCACCT**C**CCCGGCGT	128

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency THR233ILE ACA to ATA	CTGCCTCCTCCCATACTTGGCTCTATTCTGCTTCTCTACAGGC TGTGGACATACTCAAGA**C**AGAGCGGCTGGGACACGGCTACC ACACCCTGGAAGACCAGGCCCTTTATAACAGGCTGCG	129
	CGCAGCCTGTTATAAAGGGCCTGGTCTTCCAGGGTGTGGTAG CCGTGTCCCAGCCGCTCT**G**TCTTGAGTATGTCCACAGCCTGT AGAGAAGCAGAATAGAGCCAAGTATGGGAGGAGGCAG	130
	ACTCAAGA**C**AGAGCGGC	131
	GCCGCTCT**G**TCTTGAGT	132
Adenosine deaminase deficiency ARG253PRO CGG to CCG	CAGAGCGGCTGGGACACGGCTACCACACCCTGGAAGACCAG GCCCTTTATAACAGGCTGC**G**GCAGGAAAACATGCACTTCGAG GTAAGCGGGCCAGGGAGTGGGGAGGAACCATCCCCGGC	133
	GCCGGGGATGGTTCCTCCCCACTCCCTGGCCCGCTTACCTC GAAGTGCATGTTTTCCTGC**C**GCAGCCTGTTATAAAGGGCCTG GTCTTCCAGGGTGTGGTAGCCGTGTCCCAGCCGCTCTG	134
	CAGGCTGC**G**GCAGGAAA	135
	TTTCCTGC**C**GCAGCCTG	136
Adenosine deaminase deficiency GLN254TERM CAG to TAG	GAGCGGCTGGGACACGGCTACCACACCCTGGAAGACCAGGC CCTTTATAACAGGCTGCGG**C**AGGAAAACATGCACTTCGAGGT AAGCGGGCCAGGGAGTGGGGAGGAACCATCCCCGGCTG	137
	CAGCCGGGGATGGTTCCTCCCCACTCCCTGGCCCGCTTACC TCGAAGTGCATGTTTTCCT**G**CCGCAGCCTGTTATAAAGGGCC TGGTCTTCCAGGGTGTGGTAGCCGTGTCCCAGCCGCTC	138
	GGCTGCGG**C**AGGAAAAC	139
	GTTTTCCT**G**CCGCAGCC	140
Adenosine deaminase deficiency PRO274LEU CCG to CTG	CCACACACCTGCTCTTCCAGATCTGCCCCTGGTCCAGCTACC TCACTGGTGCCTGGAAGC**C**GGACACGGAGCATGCAGTCATT CGGTGAGCTCTGTTCCCCTGGGCCTGTTCAATTTTGTT	141
	AACAAAATTGAACAGGCCCAGGGGAACAGAGCTCACCGAATG ACTGCATGCTCCGTGTCC**G**GCTTCCAGGCACCAGTGAGGTA GCTGGACCAGGGGCAGATCTGGAAGAGCAGGTGTGTGG	142
	CTGGAAGC**C**GGACACGG	143
	CCGTGTCC**G**GCTTCCAG	144

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency SER291LEU TCG to TTG	GGAGGCTGATTCTCTCCTCCCTCTTCTGCAGGCTCAAAA ATGACCAGGCTAACTACT**C**GCTCAACACAGATGACCCGCTCA TCTTCAAGTCCACCCTGGACACTGATTACCAGATGAC	145
	GTCATCTGGTAATCAGTGTCCAGGGTGGACTTGAAGATGAGC GGGTCATCTGTGTTGAGC**G**AGTAGTTAGCCTGGTCATTTTTGA GCCTGCAGAAGAGGGAGGAGGAGAGAATCAGCCTCC	146
	TAACTACT**C**GCTCAACA	147
	TGTTGAGC**G**AGTAGTTA	148
Adenosine deaminase deficiency PRO297GLN CCG to CAG	CCTCCCTCTTCTGCAGGCTCAAAAATGACCAGGCTAACTACT CGCTCAACACAGATGACC**C**GCTCATCTTCAAGTCCACCCTGG ACACTGATTACCAGATGACCAAACGGGACATGGGCTT	149
	AAGCCCATGTCCCGTTTGGTCATCTGGTAATCAGTGTCCAGG GTGGACTTGAAGATGAGC**G**GGTCATCTGTGTTGAGCGAGTAG TTAGCCTGGTCATTTTTGAGCCTGCAGAAGAGGGAGG	150
	AGATGACC**C**GCTCATCT	151
	AGATGAGC**G**GGTCATCT	152
Adenosine deaminase deficiency LEU304ARG CTG to CGG	AAAATGACCAGGCTAACTACTCGCTCAACACAGATGACCCGC TCATCTTCAAGTCCACCC**T**GGACACTGATTACCAGATGACCAA ACGGGACATGGGCTTTACTGAAGAGGAGTTTAAAAG	153
	CTTTTAAACTCCTCTTCAGTAAAGCCCATGTCCCGTTTGGTCA TCTGGTAATCAGTGTCC**A**GGGTGGACTTGAAGATGAGCGGGT CATCTGTGTTGAGCGAGTAGTTAGCCTGGTCATTTT	154
	GTCCACCC**T**GGACACTG	155
	CAGTGTCC**A**GGGTGGAC	156
Adenosine deaminase deficiency ALA329VAL C-to-T at base 1081	GCCTTCTTTGTTCTCTGGTTCCATGTTGTCTGCCATTCTGGCC TTTCCAGAACATCAATG**C**GGCCAAATCTAGTTTCCTCCCAGAA GATGAAAAGAGGGAGCTTCTCGACCTGCTCTATAA	157
	TTATAGAGCAGGTCGAGAAGCTCCCTCTTTTCATCTTCTGGGA GGAAACTAGATTTGGCC**G**CATTGATGTTCTGGAAAGGCCAGA ATGGCAGACAACATGGAACCAGAGAACAAAGAAGGC	158
	CATCAATG**C**GGCCAAAT	159
	ATTTGGCC**G**CATTGATG	160

EXAMPLE 5
P53 Mutations

The p53 gene codes for a protein that acts as a transcription factor and serves as a key regulator of the cell cycle. Mutation in this gene is probably the most significant genetic change characterizing the transformation of cells from normalcy to malignancy.

Inactivation of p53 by mutation disrupts the cell cycle which, in turn, sets the stage for tumor formation. Mutations in the p53 gene are among the most commonly diagnosed genetic disorders, occuring in as many as 50% of cancer patients. For some types of cancer, most notably of the breast, lung and colon, p53 mutations are the predominant genetic alternations found thus far. These mutations are associated with genomic instability and thus an increased susceptibility to cancer. Some p53 lesions result in malignancies that are resistant to the most widely used therapeutic regimens and therefore demand more aggressive treatment.

That p53 is associated with different malignant tumors is illustrated in the Li-Fraumeni autosomal dominant hereditary disorder characterized by familial multiple tumors due to mutation in the p53 gene. Affected individuals can develop one or more tumors, including: brain (12%); soft-tissue sarcoma (12%); breast cancer (25%); adrenal tumors (1%); bone cancer (osteosarcoma) (6%); cancer of the lung, prostate, pancreas, and colon as well as lymphoma and melanoma can also occur.

Certain of the most frequently mutated codons are codons 175, 248 and 273, however a variety of oligonucleotides are described below in the atttached table.

Table 11
p53 Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
In 2 families with Li-Fraumeni syndrome, there was a C-to-T mutation at the first nucleotide of codon 248 which changed arginine to tryptophan.	GACTGTACCACCATCCACTACAACTACATGTGTAACAGTTCCT GCATGGGCGGCATGAACCGGAGGCCCATCCTCACCATCATC ACACTGGAAGACTCCAGGTCAGGAGCCACTTGCCACC	161
	GGTGGCAAGTGGCTCCTGACCTGGAGTCTTCCAGTGTGATGA TGGTGAGGATGGGCCTCC**G**GTTCATGCCGCCCATGCAGGAA CTGTTACACATGTAGTTGTAGTGGATGGTGGTACAGTC	162
	GCATGAAC**C**GGAGGCCC	163

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GGGCCTCC**G**GTTCATGC	164
In a family with the Li-Fraumeni syndrome, a G-to-A mutation at the first nucleotide of codon 258 resulting in the substitution of lysine for glutamic acid.	TGTAACAGTTCCTGCATGGGCGGCATGAACCGGAGGCCCATCCTCACCATCATCACACTG**G**AAGACTCCAGGTCAGGAGCCACTTGCCACCCTGCACACTGGCCTGCTGTGCCCCAGCCTC	165
	GAGGCTGGGGCACAGCAGGCCAGTGTGCAGGGTGGCAAGTGGCTCCTGACCTGGAGTCTT**C**CAGTGTGATGATGGTGAGGATGGGCCTCCGGTTCATGCCGCCCATGCAGGAACTGTTACA	166
	TCACACTG**G**AAGACTCC	167
	GGAGTCTT**C**CAGTGTGA	168
In a family with the Li-Fraumeni syndrome, a G-to-T mutation at the first nucleotide of codon 245 resulting in the substitution of cysteine for glycine.	GTTGGCTCTGACTGTACCACCATCCACTACAACTACATGTGTAACAGTTCCTGCATGGGC**G**GCATGAACCGGAGGCCCATCCTCACCATCATCACACTGGAAGACTCCAGGTCAGGAGCCA	169
A gly245-to-ser, GGC-to-AGC, mutation was found in a patient in whom osteosarcoma was diagnosed at the age of 18 years.	TGGCTCCTGACCTGGAGTCTTCCAGTGTGATGATGGTGAGGATGGGCCTCCGGTTCATGC**C**GCCCATGCAGGAACTGTTACACATGTAGTTGTAGTGGATGGTGGTACAGTCAGAGCCAAC	170
	GCATGGGC**G**GCATGAAC	171
	GTTCATGC**C**GCCCATGC	172
In a family with the Li-Fraumeni syndrome, a germline mutation at codon 252: a T-to-C change at the second position resulted in substitution of proline for leucine.	TCCACTACAACTACATGTGTAACAGTTCCTGCATGGGCGGCATGAACCGGAGGCCCATCC**T**CACCATCATCACACTGGAAGACTCCAGGTCAGGAGCCACTTGCCACCCTGCACACTGGCC	173
	GGCCAGTGTGCAGGGTGGCAAGTGGCTCCTGACCTGGAGTCTTCCAGTGTGATGATGGTG**A**GGATGGGCCTCCGGTTCATGCCGCCCATGCAGGAACTGTTACACATGTAGTTGTAGTGGA	174
	GCCCATCC**T**CACCATCA	175
	TGATGGTG**A**GGATGGGC	176

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Researchers analyzed for mutations in p53 hepatocellular carcinomas from patients in Qidong, an area of high incidence in China, in which both hepatitis B virus and aflatoxin B1 are risk factors. Eight of 16 tumors had a point mutation at the third base position of codon 249. The G-to-T mutation at codon 249 led to a change from arginine to serine (AGG to AGT).	TACCACCATCCACTACAACTACATGTGTAACAGTTCCTGCATG GGCGGCATGAACCGGAG**G**CCCATCCTCACCATCATCACACT GGAAGACTCCAGGTCAGGAGCCACTTGCCACCCTGCA	177
	TGCAGGGTGGCAAGTGGCTCCTGACCTGGAGTCTTCCAGTG TGATGATGGTGAGGATGGG**C**CTCCGGTTCATGCCGCCCATG CAGGAACTGTTACACATGTAGTTGTAGTGGATGGTGGTA	178
	AACCGGAG**G**CCCATCCT	179
	AGGATGGG**C**CTCCGGTT	180
In cases of hepatocellular carcinoma in southern Africa, a G-to-T substitution in codon 157 resulting in a change from valine to phenylalanine.	CTGGCCAAGACCTGCCCTGTGCAGCTGTGGGTTGATTC**C**ACA CCCCCGCCCGGCACCCGC**G**TCCGCGCCATGGCCATCTACAA GCAGTCACAGCACATGACGGAGGTTGTGAGGCGCTGCC	181
	GGCAGCGCCTCACAACCTCCGTCATGTGCTGTGACTGCTTGT AGATGGCCATGGCGCGGA**C**GCGGGTGCCGGGCGGGGGTGT GGAATCAACCCACAGCTGCACAGGGCAGGTCTTGGCCAG	182
	GCACCCGC**G**TCCGCGCC	183
	GGCGCGGA**C**GCGGGTGC	184
In a family with Li-Fraumeni in which noncancerous skin fibroblasts from affected individuals showed an unusual radiation-resistant phenotype, a point mutation in codon 245 of the P53 gene. A change from GGC to GAC predicted substitution of aspartic acid for glycine.	TTGGCTCTGACTGTACCACCATCCACTACAACTACATGTGTAA CAGTTCCTGCATGGGCG**G**CATGAACCGGAGGCCCATCCTCA CCATCATCACACTGGAAGACTCCAGGTCAGGAGCCAC	185
	GTGGCTCCTGACCTGGAGTCTTCCAGTGTGATGATGGTGAGG ATGGGCCTCCGGTTCATG**C**CGCCCATGCAGGAACTGTTACAC ATGTAGTTGTAGTGGATGGTGGTACAGTCAGAGCCAA	186
	CATGGGCG**G**CATGAACC	187
	GGTTCATG**C**CGCCCATG	188

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
In 2 of 8 families with Li-Fraumeni syndrome, a mutation in codon 248: a CGG-to-CAG change resulting in substitution of glutamine for arginine.	ACTGTACCACCATCCACTACAACTACATGTGTAACAGTTCCTG CATGGGCGGCATGAACC**G**GAGGCCCATCCTCACCATCATCA CACTGGAAGACTCCAGGTCAGGAGCCACTTGCCACCC	189
	GGGTGGCAAGTGGCTCCTGACCTGGAGTCTTCCAGTGTGAT GATGGTGAGGATGGGCCTC**C**GGTTCATGCCGCCCATGCAGG AACTGTTACACATGTAGTTGTAGTGGATGGTGGTACAGT	190
	CATGAACC**G**GAGGCCCA	191
	TGGGCCTC**C**GGTTCATG	192
In 9 members of an extended family with Li-Fraumeni syndrome, a germline mutation at codon 133 (ATG-to-ACG), resulted in the substitution of threonine for methionine (M133T), and completely cosegregated with the cancer syndrome.	CCCTGACTTTCAACTCTGTCTCCTTCCTCTTCCTACAGTACTC CCCTGCCCTCAACAAGA**T**GTTTTGCCAACTGGCCAAGACCTG CCCTGTGCAGCTGTGGGTTGATTCCACACCCCCGCC	193
	GGCGGGGGTGTGGAATCAACCCACAGCTGCACAGGGCAGGT CTTGGCCAGTTGGCAAAAC**A**TCTTGTTGAGGGCAGGGGAGTA CTGTAGGAAGAGGAAGGAGACAGAGTTGAAAGTCAGGG	194
	CAACAAGA**T**GTTTTGCC	195
	GGCAAAAC**A**TCTTGTTG	196
In 1 pedigree consistent with the Li-Fraumeni syndrome, a germline G-to-T transversion at codon 272 (valine to leucine) was found.	TCTTGCTTCTCTTTTCCTATCCTGAGTAGTGGTAATCTACTGG GACGGAACAGCTTTGAG**G**TGCGTGTTTGTGCCTGTCCTGGGA GAGACCGGCGCACAGAGGAAGAGAATCTCCGCAAGA	197
	TCTTGCGGAGATTCTCTTCCTCTGTGCGCCGGTCTCTCCCAG GACAGGCACAAACACGCA**C**CTCAAAGCTGTTCCGTCCCAGTA GATTACCACTACTCAGGATAGGAAAAGAGAAGCAAGA	198
	GCTTTGAG**G**TGCGTGTT	199
	AACACGCA**C**CTCAAAGC	200
A ser241-to-phe mutation due to a TCC-to-TTC change was found in a patient with hepatoblastoma and multiple foci of osteosarcoma.	TTATCTCCTAGGTTGGCTCTGACTGTACCACCATCCACTACAA CTACATGTGTAACAGTT**C**CTGCATGGGCGGCATGAACCGGAG GCCCATCCTCACCATCATCACACTGGAAGACTCCAG	201
	CTGGAGTCTTCCAGTGTGATGATGGTGAGGATGGGCCTCCG GTTCATGCCGCCCATGCAG**G**AACTGTTACACATGTAGTTGTA GTGGATGGTGGTACAGTCAGAGCCAACCTAGGAGATAA	202

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TAACAGTT**C**CTGCATGG	203
	CCATGCAG**G**AACTGTTA	204
An AAG-to-TAG change of codon 120, resulting in conversion from lysine to a stop codon, was found in a patient with osteosarcoma and adenocarcinoma of the lung at age 18 and brain tumor (glioma) at the age of 27.	CAGAAAACCTACCAGGGCAGCTACGGTTTCCGTCTGGGCTTC TTGCATTCTGGGACAGCC**A**AGTCTGTGACTTGCACGGTCAGT TGCCCTGAGGGGCTGGCTTCCATGAGACTTCAATGCC	205
	GGCATTGAAGTCTCATGGAAGCCAGCCCCTCAGGGCAACTG ACCGTGCAAGTCACAGACT**T**GGCTGTCCCAGAATGCAAGAAG CCCAGACGGAAACCGTAGCTGCCCTGGTAGGTTTTCTG	206
	GGACAGCC**A**AGTCTGTG	207
	CACAGACT**T**GGCTGTCC	208
A CGG-to-TGG change at codon 282, resulting in the substitution of tryptophan for arginine, was found in a patient who developed osteosarcoma at the age of 10 years.	GGTAATCTACTGGGACGGAACAGCTTTGAGGTGCGTGTTTGT GCCTGTCCTGGGAGAGAC**C**GGCGCACAGAGGAAGAGAATCT CCGCAAGAAAGGGGAGCCTCACCACGAGCTGCCCCCAG	209
	CTGGGGGCAGCTCGTGGTGAGGCTCCCCTTTCTTGCGGAGA TTCTCTTCCTCTGTGCGCC**G**GTCTCTCCCAGGACAGGCACAA ACACGCACCTCAAAGCTGTTCCGTCCCAGTAGATTACC	210
	GGAGAGAC**C**GGCGCACA	211
	TGTGCGCC**G**GTCTCTCC	212
In 5 of 6 anaplastic carcinomas of the thyroid and in an anaplastic carcinoma thyroid cell line ARO, a CGT-to-CAT mutation converted arginine-273 to histidine.	GCTTCTCTTTTCCTATCCTGAGTAGTGGTAATCTACTGGGACG GAACAGCTTTGAGGTGC**G**TGTTTGTGCCTGTCCTGGGAGAGA CCGGCGCACAGAGGAAGAGAATCTCCGCAAGAAAGG	213
	CCTTTCTTGCGGAGATTCTCTTCCTCTGTGCGCCGGTCTCTC CCAGGACAGGCACAAACA**C**GCACCTCAAAGCTGTTCCGTCCC AGTAGATTACCACTACTCAGGATAGGAAAAGAGAAGC	214
	TGAGGTGC**G**TGTTTGTG	215
	CACAAACA**C**GCACCTCA	216

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
A germline GGA-to-GTA mutation resulting in a change of glycine-325 to valine was found in a patient who had non-Hodgkin lymphoma diagnosed at age 17 and colon carcinoma at age 26.	TCCTAGCACTGCCCAACAACACCAGCTCCTCTCCCCAGCCAA AGAAGAAACCACTGGATG**G**AGAATATTTCACCCTTCAGGTACT AAGTCTTGGGACCTCTTATCAAGTGGAAAGTTTCCA	217
	TGGAAACTTTCCACTTGATAAGAGGTCCCAAGACTTAGTACCT GAAGGGTGAAATATTCT**C**CATCCAGTGGTTTCTTCTTTGGCTG GGGAGAGGAGCTGGTGTTGTTGGGCAGTGCTAGGA	218
	ACTGGATG**G**AGAATATT	219
	AATATTCT**C**CATCCAGT	220
CGC-CCC Arg-72 to Pro association with Lung cancer	AATGGTTCACTGAAGACCCAGGTCCAGATGAAGCTCCCAGAA TGCCAGAGGCTGCTCCCC**G**CGTGGCCCCTGCACCAGCAGCT CCTACACCGGCGGCCCCTGCACCAGCCCCCTCCTGGCC	221
	GGCCAGGAGGGGGCTGGTGCAGGGGCCGCCGGTGTAGGAG CTGCTGGTGCAGGGGCCACG**C**GGGGAGCAGCCTCTGGCATT CTGGGAGCTTCATCTGGACCTGGGTCTTCAGTGAACCATT	222
	TGCTCCCC**G**CGTGGCCC	223
	GGGCCACG**C**GGGGAGCA	224
CCG-CTG Pro-82 to Leu Breast cancer	AAGCTCCCAGAATGCCAGAGGCTGCTCCCCGCGTGGCCCCT GCACCAGCAGCTCCTACAC**C**GGCGGCCCCTGCACCAGCCCC CTCCTGGCCCCTGTCATCTTCTGTCCCTTCCCAGAAAAC	225
	GTTTTCTGGGAAGGGACAGAAGATGACAGGGGCCAGGAGGG GGCTGGTGCAGGGGCCGCC**G**GTGTAGGAGCTGCTGGTGCA GGGGCCACGCGGGGAGCAGCCTCTGGCATTCTGGGAGCTT	226
	TCCTACAC**C**GGCGGCCC	227
	GGGCCGCC**G**GTGTAGGA	228
cCAA-TAA Gln-136 to Term Li-Fraumeni syndrome	TTCAACTCTGTCTCCTTCCTCTTCCTACAGTACTCCCCTGCCC TCAACAAGATGTTTTGC**C**AACTGGCCAAGACCTGCCCTGTGC AGCTGTGGGTTGATTC**C**ACACCCCCGCCCGGCACCC	229
	GGGTGCCGGGCGGGGGTGTGGAATCAACCCACAGCTGCACA GGGCAGGTCTTGGCCAGTT**G**GCAAAACATCTTGTTGAGGGCA GGGGAGTACTGTAGGAAGAGGAAGGAGACAGAGTTGAA	230
	TGTTTTGC**C**AACTGGCC	231
	GGCCAGTT**G**GCAAAACA	232

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
TGC-TAC Cys-141 to Tyr Li-Fraumeni syndrome	TCCTCTTCCTACAGTACTCCCCTGCCCTCAACAAGATGTTTTG CCAACTGGCCAAGACCT**G**CCCTGTGCAGCTGTGGGTTGATTC **C**ACACCCCCGCCCGGCACCCGCGTCCGCGCCATGGC	233
	GCCATGGCGCGGACGCGGGTGCCGGGCGGGGGTGTGGAAT CAACCCACAGCTGCACAGGG**C**AGGTCTTGGCCAGTTGGCAA AACATCTTGTTGAGGGCAGGGGAGTACTGTAGGAAGAGGA	234
	CAAGACCT**G**CCCTGTGC	235
	GCACAGGG**C**AGGTCTTG	236
aCCC-TCC Pro-151 to Ser Li-Fraumeni syndrome	AACAAGATGTTTTGCCAACTGGCCAAGACCTGCCCTGTGCAG CTGTGGGTTGATTC**C**ACA**C**CCCCGCCCGGCACCCGCGTCCG CGCCATGGCCATCTACAAGCAGTCACAGCACATGACGG	237
	CCGTCATGTGCTGTGACTGCTTGTAGATGGCCATGGCGCGG ACGCGGGTGCCGGGCGGGG**G**TGTGGAATCAACCCACAGCT GCACAGGGCAGGTCTTGGCCAGTTGGCAAAACATCTTGTT	238
	ATTCCACA**C**CCCCGCCC	239
	GGGCGGGG**G**TGTGGAAT	240
CCG-CTG Pro-152 to Leu Adrenocortical carcinoma	AGATGTTTTGCCAACTGGCCAAGACCTGCCCTGTGCAGCTGT GGGTTGATTC**C**ACACCCC**C**GCCCGGCACCCGCGTCCGCGCC ATGGCCATCTACAAGCAGTCACAGCACATGACGGAGGT	241
	ACCTCCGTCATGTGCTGTGACTGCTTGTAGATGGCCATGGCG CGGACGCGGGTGCCGGGC**G**GGGGTGTGGAATCAACCCACA GCTGCACAGGGCAGGTCTTGGCCAGTTGGCAAAACATCT	242
	CACACCCC**C**GCCCGGCA	243
	TGCCGGGC**G**GGGGTGTG	244
GGC-GTC Gly-154 to Val Glioblastoma	TTTGCCAACTGGCCAAGACCTGCCCTGTGCAGCTGTGGGTTG ATTC**C**ACACCCCCGCCCG**G**CACCCGCGTCCGCGCCATGGCC ATCTACAAGCAGTCACAGCACATGACGGAGGTTGTGAG	245
	CTCACAACCTCCGTCATGTGCTGTGACTGCTTGTAGATGGCC ATGGCGCGGACGCGGGTG**C**CGGGCGGGGGTGTGGAATCAA CCCACAGCTGCACAGGGCAGGTCTTGGCCAGTTGGCAAA	246
	CCCGCCCG**G**CACCCGCG	247
	CGCGGGTG**C**CGGGCGGG	248
CGC-CAC Arg-175 to His Li-Fraumeni syndrome	CCCGCGTCCGCGCCATGGCCATCTACAAGCAGTCACAGCAC ATGACGGAGGTTGTGAGGC**G**CTGCCCCCACCATGAGCGCTG CTCAGATAGCGATGGTGAGCAGCTGGGGCTGGAGAGACG	249

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CGTCTCTCCAGCCCCAGCTGCTCACCATCGCTATCTGAGCAG CGCTCATGGTGGGGGCAG**C**GCCTCACAACCTCCGTCATGTG CTGTGACTGCTTGTAGATGGCCATGGCGCGGACGCGGG	250
	TGTGAGGC**G**CTGCCCCC	251
	GGGGGCAG**C**GCCTCACA	252
tGAG-AAG Glu-180 to Lys Li-Fraumeni syndrome	ATGGCCATCTACAAGCAGTCACAGCACATGACGGAGGTTGTG AGGCGCTGCCCCCACCAT**G**AGCGCTGCTCAGATAGCGATGG TGAGCAGCTGGGGCTGGAGAGACGACAGGGCTGGTTGC	253
	GCAACCAGCCCTGTCGTCTCTCCAGCCCCAGCTGCTCACCAT CGCTATCTGAGCAGCGCT**C**ATGGTGGGGGCAGCGCCTCACA ACCTCCGTCATGTGCTGTGACTGCTTGTAGATGGCCAT	254
	CCCACCAT**G**AGCGCTGC	255
	GCAGCGCT**C**ATGGTGGG	256
gCGC-TGC Arg-181 to Cys Breast cancer	GCCATCTACAAGCAGTCACAGCACATGACGGAGGTTGTGAGG CGCTGCCCCCACCATGAG**C**GCTGCTCAGATAGCGATGGTGA GCAGCTGGGGCTGGAGAGACGACAGGGCTGGTTGCCCA	257
	TGGGCAACCAGCCCTGTCGTCTCTCCAGCCCCAGCTGCTCA CCATCGCTATCTGAGCAGC**G**CTCATGGTGGGGGCAGCGCCT CACAACCTCCGTCATGTGCTGTGACTGCTTGTAGATGGC	258
	ACCATGAG**C**GCTGCTCA	259
	TGAGCAGC**G**CTCATGGT	260
CGC-CAC Arg-81 to His Breast cancer	CCATCTACAAGCAGTCACAGCACATGACGGAGGTTGTGAGGC GCTGCCCCCACCATGAGC**G**CTGCTCAGATAGCGATGGTGAG CAGCTGGGGCTGGAGAGACGACAGGGCTGGTTGCCCAG	261
	CTGGGCAACCAGCCCTGTCGTCTCTCCAGCCCCAGCTGCTC ACCATCGCTATCTGAGCAG**C**GCTCATGGTGGGGGCAGCGCC TCACAACCTCCGTCATGTGCTGTGACTGCTTGTAGATGG	262
	CCATGAGC**G**CTGCTCAG	263
	CTGAGCAG**C**GCTCATGG	264
CAT-CGT His-193 to Arg Li-Fraumeni syndrome	CCAGGGTCCCCAGGCCTCTGATTCCTCACTGATTGCTCTTAG GTCTGGCCCCTCCTCAGC**A**TCTTATCCGAGTGGAAGGAAATT TGCGTGTGGAGTATTTGGATGACAGAAACACTTTTCG	265
	CGAAAAGTGTTTCTGTCATCCAAATACTCCACACGCAAATTTC CTTCCACTCGGATAAGA**T**GCTGAGGAGGGGCCAGACCTAAGA GCAATCAGTGAGGAATCAGAGGCCTGGGGACCCTGG	266

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TCCTCAGC**A**TCTTATCC	267
	GGATAAGA**T**GCTGAGGA	268
cCGA-TGA Arg-196 to Term Adrenocortical carcinoma	CCCAGGCCTCTGATTCCTCACTGATTGCTCTTAGGTCTGGCC CCTCCTCAGCATCTTATC**C**GAGTGGAAGGAAATTTGCGTGTG GAGTATTTGGATGACAGAAACACTTTTCGACATAGTG	269
	CACTATGTCGAAAAGTGTTTCTGTCATCCAAATACTCCACACG CAAATTTCCTTCCACTC**G**GATAAGATGCTGAGGAGGGGCCAG ACCTAAGAGCAATCAGTGAGGAATCAGAGGCCTGGG	270
	ATCTTATC**C**GAGTGGAA	271
	TTCCACTC**G**GATAAGAT	272
cAGA-TGA Arg-209 to Term Li-Fraumeni syndrome	GCCCCTCCTCAGCATCTTATCCGAGTGGAAGGAAATTTGCGT GTGGAGTATTTGGATGAC**A**GAAACACTTTTCGACATAGTGTG GTGGTGCCCTATGAGCCGCCTGAGGTCTGGTTTGCAA	273
	TTGCAAACCAGACCTCAGGCGGCTCATAGGGCACCACCACA CTATGTCGAAAAGTGTTTC**T**GTCATCCAAATACTCCACACGCA AATTTCCTTCCACTCGGATAAGATGCTGAGGAGGGGC	274
	TGGATGAC**A**GAAACACT	275
	AGTGTTTC**T**GTCATCCA	276
tCGA-TGA Arg-213 to Term Li-Fraumeni syndrome	CATCTTATCCGAGTGGAAGGAAATTTGCGTGTGGAGTATTTG GATGACAGAAACACTTTT**C**GACATAGTGTGGTGGTGCCCTAT GAGCCGCCTGAGGTCTGGTTTGCAACTGGGGTCTCTG	277
	CAGAGACCCCAGTTGCAAACCAGACCTCAGGCGGCTCATAG GGCACCACCACACTATGTC**G**AAAAGTGTTTCTGTCATCCAAAT ACTCCACACGCAAATTTCCTTCCACTCGGATAAGATG	278
	ACACTTTT**C**GACATAGT	279
	ACTATGTC**G**AAAAGTGT	280
gCCC-TCC Pro-219 to Ser Adrenocortical carcinoma	GGAAATTTGCGTGTGGAGTATTTGGATGACAGAAACACTTTTC GACATAGTGTGGTGGTG**C**CCTATGAGCCGCCTGAGGTCTGG TTTGCAACTGGGGTCTCTGGGAGGAGGGGTTAAGGGT	281
	ACCCTTAACCCCTCCTCCCAGAGACCCCAGTTGCAAACCAGA CCTCAGGCGGCTCATAGG**G**CACCACCACACTATGTCGAAAAG TGTTTCTGTCATCCAAATACTCCACACGCAAATTTCC	282
	TGGTGGTG**C**CCTATGAG	283
	CTCATAGG**G**CACCACCA	284

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
TAT-TGT Tyr-220 to Cys Li-Fraumeni syndrome	ATTTGCGTGTGGAGTATTTGGATGACAGAAACACTTTTCGACA TAGTGTGGTGGTGCCCT**A**TGAGCCGCCTGAGGTCTGGTTTG CAACTGGGGTCTCTGGGAGGAGGGGTTAAGGGTGGTT	285
	AACCACCCTTAACCCCTCCTCCCAGAGACCCCAGTTGCAAAC CAGACCTCAGGCGGCTCA**T**AGGGCACCACCACACTATGTCG AAAAGTGTTTCTGTCATCCAAATACTCCACACGCAAAT	286
	GGTGCCCT**A**TGAGCCGC	287
	GCGGCTCA**T**AGGGCACC	288
cTCT-ACT Ser-227 to Thr Rhabdomyosarcoma	CACAGGTCTCCCCAAGGCGCACTGGCCTCATCTTGGGCCTG TGTTATCTCCTAGGTTGGC**T**CTGACTGTACCACCATCCACTAC AACTACATGTGTAACAGTTCCTGCATGGGCGGCATGA	289
	TCATGCCGCCCATGCAGGAACTGTTACACATGTAGTTGTAGT GGATGGTGGTACAGTCAG**A**GCCAACCTAGGAGATAACACAG GCCCAAGATGAGGCCAGTGCGCCTTGGGGAGACCTGTG	290
	AGGTTGGC**T**CTGACTGT	291
	ACAGTCAG**A**GCCAACCT	292
cCAC-AAC His-233 to Asn Glioma	GCACTGGCCTCATCTTGGGCCTGTGTTATCTCCTAGGTTGGC TCTGACTGTACCACCATC**C**ACTACAACTACATGTGTAACAGTT CCTGCATGGGCGGCATGAACCGGAGGCCCATCCTCA	293
	TGAGGATGGGCCTCCGGTTCATGCCGCCCATGCAGGAACTG TTACACATGTAGTTGTAGT**G**GATGGTGGTACAGTCAGAGCCA ACCTAGGAGATAACACAGGCCCAAGATGAGGCCAGTGC	294
	CCACCATC**C**ACTACAAC	295
	GTTGTAGT**G**GATGGTGG	296
cAAC-GAC Asn-235 to Asp Adrenocortical carcinoma	GCCTCATCTTGGGCCTGTGTTATCTCCTAGGTTGGCTCTGAC TGTACCACCATCCACTAC**A**ACTACATGTGTAACAGTTCCTGCA TGGGCGGCATGAACCGGAGGCCCATCCTCACCATCA	297
	TGATGGTGAGGATGGGCCTCCGGTTCATGCCGCCCATGCAG GAACTGTTACACATGTAGT**T**GTAGTGGATGGTGGTACAGTCA GAGCCAACCTAGGAGATAACACAGGCCCAAGATGAGGC	298
	TCCACTAC**A**ACTACATG	299
	CATGTAGT**T**GTAGTGGA	300
AAC-AGC Asn-235 to Ser Rhabdomyosarcoma	CCTCATCTTGGGCCTGTGTTATCTCCTAGGTTGGCTCTGACT GTACCACCATCCACTACA**A**CTACATGTGTAACAGTTCCTGCAT GGGCGGCATGAACCGGAGGCCCATCCTCACCATCAT	301

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATGATGGTGAGGATGGGCCTCCGGTTCATGCCGCCCATGCA GGAACTGTTACACATGTAG**T**TGTAGTGGATGGTGGTACAGTC AGAGCCAACCTAGGAGATAACACAGGCCCAAGATGAGG	302
	CCACTACA**A**CTACATGT	303
	ACATGTAG**T**TGTAGTGG	304
ATCc-ATG Ile-251 to Met Glioma	CATCCACTACAACTACATGTGTAACAGTTCCTGCATGGGCGG CATGAACCGGAGGCCCAT**C**CTCACCATCATCACACTGGAAGA CTCCAGGTCAGGAGCCACTTGCCACCCTGCACACTGG	305
	CCAGTGTGCAGGGTGGCAAGTGGCTCCTGACCTGGAGTCTT CCAGTGTGATGATGGTGAG**G**ATGGGCCTCCGGTTCATGCCG CCCATGCAGGAACTGTTACACATGTAGTTGTAGTGGATG	306
	AGGCCCAT**C**CTCACCAT	307
	ATGGTGAG**G**ATGGGCCT	308
ACA-ATA Thr-256 to Ile Glioblastoma	ACATGTGTAACAGTTCCTGCATGGGCGGCATGAACCGGAGG CCCATCCTCACCATCATCA**C**ACTGGAAGACTCCAGGTCAGGA GCCACTTGCCACCCTGCACACTGGCCTGCTGTGCCCCA	309
	TGGGGCACAGCAGGCCAGTGTGCAGGGTGGCAAGTGGCTCC TGACCTGGAGTCTTCCAGT**G**TGATGATGGTGAGGATGGGCCT CCGGTTCATGCCGCCCATGCAGGAACTGTTACACATGT	310
	CATCATCA**C**ACTGGAAG	311
	CTTCCAGT**G**TGATGATG	312
CTG-CAG Leu-257 to Gln Li-Fraumeni syndrome	TGTGTAACAGTTCCTGCATGGGCGGCATGAACCGGAGGCCC ATCCTCACCATCATCACAC**T**GGAAGACTCCAGGTCAGGAGCC ACTTGCCACCCTGCACACTGGCCTGCTGTGCCCCAGCC	313
	GGCTGGGGCACAGCAGGCCAGTGTGCAGGGTGGCAAGTGG CTCCTGACCTGGAGTCTTCC**A**GTGTGATGATGGTGAGGATGG GCCTCCGGTTCATGCCGCCCATGCAGGAACTGTTACACA	314
	CATCACAC**T**GGAAGACT	315
	AGTCTTCC**A**GTGTGATG	316
CTG-CCG Leu-265 to Pro Li-Fraumeni syndrome	GACCTGATTTCCTTACTGCCTCTTGCTTCTCTTTTCCTATCCT GAGTAGTGGTAATCTAC**T**GGGACGGAACAGCTTTGAGGTGCG TGTTTGTGCCTGTCCTGGGAGAGACCGGCGCACAGA	317
	TCTGTGCGCCGGTCTCTCCCAGGACAGGCACAAACACGCAC CTCAAAGCTGTTCCGTCCC**A**GTAGATTACCACTACTCAGGAT AGGAAAAGAGAAGCAAGAGGCAGTAAGGAAATCAGGTC	318

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TAATCTAC**T**GGGACGGA	319
	TCCGTCCC**A**GTAGATTA	320
gCGT-TGT Arg-273 to Cys Li-Fraumeni syndrome	TGCTTCTCTTTTCCTATCCTGAGTAGTGGTAATCTACTGGGAC GGAACAGCTTTGAGGTG**C**GTGTTTGTGCCTGTCCTGGGAGA GACCGGCGCACAGAGGAAGAGAATCTCCGCAAGAAAG	321
	CTTTCTTGCGGAGATTCTCTTCCTCTGTGCGCCGGTCTCTCC CAGGACAGGCACAAACAC**G**CACCTCAAAGCTGTTCCGTCCCA GTAGATTACCACTACTCAGGATAGGAAAAGAGAAGCA	322
	TTGAGGTG**C**GTGTTTGT	323
	ACAAACAC**G**CACCTCAA	324
TGT-TAT Cys-275 to Tyr Li-Fraumeni syndrome	CTTTTCCTATCCTGAGTAGTGGTAATCTACTGGGACGGAACA GCTTTGAGGTGCGTGTTT**G**TGCCTGTCCTGGGAGAGACCGG CGCACAGAGGAAGAGAATCTCCGCAAGAAAGGGGAGCC	325
	GGCTCCCCTTTCTTGCGGAGATTCTCTTCCTCTGTGCGCCGG TCTCTCCCAGGACAGGCA**C**AAACACGCACCTCAAAGCTGTTC CGTCCCAGTAGATTACCACTACTCAGGATAGGAAAAG	326
	GCGTGTTT**G**TGCCTGTC	327
	GACAGGCA**C**AAACACGC	328
CCT-CTT Pro-278 to Leu Breast cancer	TCCTGAGTAGTGGTAATCTACTGGGACGGAACAGCTTTGAGG TGCGTGTTTGTGCCTGTC**C**TGGGAGAGACCGGCGCACAGAG GAAGAGAATCTCCGCAAGAAAGGGGAGCCTCACCACGA	329
	TCGTGGTGAGGCTCCCCTTTCTTGCGGAGATTCTCTTCCTCT GTGCGCCGGTCTCTCCCA**G**GACAGGCACAAACACGCACCTC AAAGCTGTTCCGTCCCAGTAGATTACCACTACTCAGGA	330
	TGCCTGTC**C**TGGGAGAG	331
	CTCTCCCA**G**GACAGGCA	332
AGA-AAA Arg-280 to Lys Glioma	GTAGTGGTAATCTACTGGGACGGAACAGCTTTGAGGTGCGTG TTTGTGCCTGTCCTGGGA**G**AGACCGGCGCACAGAGGAAGAG AATCTCCGCAAGAAAGGGGAGCCTCACCACGAGCTGCC	333
	GGCAGCTCGTGGTGAGGCTCCCCTTTCTTGCGGAGATTCTCT TCCTCTGTGCGCCGGTCT**C**TCCCAGGACAGGCACAAACACG CACCTCAAAGCTGTTCCGTCCCAGTAGATTACCACTAC	334
	TCCTGGGA**G**AGACCGGC	`335
	GCCGGTCT**C**TCCCAGGA	336

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
GAA-GCA Glu-286 to Ala Adrenocortical carcinoma	GGAACAGCTTTGAGGTGCGTGTTTGTGCCTGTCCTGGGAGA GACCGGCGCACAGAGGAAG**A**GAATCTCCGCAAGAAAGGGGA GCCTCACCACGAGCTGCCCCCAGGGAGCACTAAGCGAGG	337
	CCTCGCTTAGTGCTCCCTGGGGGCAGCTCGTGGTGAGGCTC CCCTTTCTTGCGGAGATTC**T**CTTCCTCTGTGCGCCGGTCTCT CCCAGGACAGGCACAAACACGCACCTCAAAGCTGTTCC	338
	AGAGGAAG**A**GAATCTCC	339
	GGAGATTC**T**CTTCCTCT	340
CGA-CCA Arg-306 to Pro Rhabdomyosarcoma	AAGAGAATCTCCGCAAGAAAGGGGAGCCTCACCACGAGCTG CCCCCAGGGAGCACTAAGC**G**AGGTAAGCAAGCAGGACAAGA AGCGGTGGAGGAGACCAAGGGTGCAGTTATGCCTCAGAT	341
	ATCTGAGGCATAACTGCACCCTTGGTCTCCTCCACCGCTTCT TGTCCTGCTTGCTTACCT**C**GCTTAGTGCTCCCTGGGGGCAGC TCGTGGTGAGGCTCCCCTTTCTTGCGGAGATTCTCTT	342
	CACTAAGC**G**AGGTAAGC	343
	GCTTACCT**C**GCTTAGTG	344
gCGA-TGA Arg-306 to Term Li-Fraumeni syndrome	GAAGAGAATCTCCGCAAGAAAGGGGAGCCTCACCACGAGCT GCCCCCAGGGAGCACTAAG**C**GAGGTAAGCAAGCAGGACAAG AAGCGGTGGAGGAGACCAAGGGTGCAGTTATGCCTCAGA	345
	TCTGAGGCATAACTGCACCCTTGGTCTCCTCCACCGCTTCTT GTCCTGCTTGCTTACCTC**G**CTTAGTGCTCCCTGGGGGCAGCT CGTGGTGAGGCTCCCCTTTCTTGCGGAGATTCTCTTC	346
	GCACTAAG**C**GAGGTAAG	347
	CTTACCTC**G**CTTAGTGC	348
gCGC-TGC Arg-337 to Cys Osteosarcoma	GGTACTGTGAATATACTTACTTCTCCCCCTCCTCTGTTGCTGC AGATCCGTGGGCGTGAG**C**GCTTCGAGATGTTCCGAGAGCTG AATGAGGCCTTGGAACTCAAGGATGCCCAGGCTGGGA	349
	TCCCAGCCTGGGCATCCTTGAGTTCCAAGGCCTCATTCAGCT CTCGGAACATCTCGAAGC**G**CTCACGCCCACGGATCTGCAGC AACAGAGGAGGGGGAGAAGTAAGTATATTCACAGTACC	350
	GGCGTGAG**C**GCTTCGAG	351
	CTCGAAGC**G**CTCACGCC	352
CTG-CCG Leu-344 to Pro Li-Fraumeni syndrome	CTCCCCCTCCTCTGTTGCTGCAGATCCGTGGGCGTGAGCGC TTCGAGATGTTCCGAGAGC**T**GAATGAGGCCTTGGAACTCAAG GATGCCCAGGCTGGGAAGGAGCCAGGGGGGAGCAGGGC	353

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GCCCTGCTCCCCCCTGGCTCCTTCCCAGCCTGGGCATCCTT GAGTTCCAAGGCCTCATTCAGCTCTCGGAACATCTCGAAGCG CTCACGCCCACGGATCTGCAGCAACAGAGGAGGGGGAG	354
	CCGAGAGCTGAATGAGG	355
	CCTCATTCAGCTCTCGG	356

EXAMPLE 6
beta globin

Hemoglobin, the major protein in the red blood cell, binds oxygen reversibly and is responsible for the cells' capacity to transport oxygen to the tissues. In adults, the major hemoglobin is hemoglobin A, a tetrameric protein consisting of two identical alpha globin chains and two beta globin chains. Disorders involving hemoglobin are among the most common genetic disorders worldwide, with approximately 5% of the world's population being carriers for clinically important hemoglobin mutations. Approximately 300,000 severely affected homozygotes or compound heterozygotes are born each year.

Mutation of the glutamic acid at position 7 in beta globin to valine causes sickle cell anemia, the clinical manifestations of which are well known. Mutations that cause absence of beta chain cause beta-zero-thalassemia. Reduced amounts of detectable beta globin causes beta-plus-thalassemia. For clinical purposes, beta-thalassemia is divided into thalassemia major (transfusion dependent), thalassemia intermedia (of intermediate severity), and thalassemia minor (asymptomatic). Patients with thalassemia major present in the first year of life with severe anemia; they are unable to maintain a hemoglobin level about 5 gm/dl.

The beta-thalassemias were among the first human genetic diseases to be examined by means of recombinant DNA analysis. Baysal et al., *Hemoglobin* 19(3-4):213-36 (1995) and others provide a compendium of mutations that result in beta-thalassemia.

Hemoglobin disorders were among the first to be considered for gene therapy. Transcriptional silencing of genes transferred into hematopoietic stem cells, however, poses one of the most significant challenges to its success. If the transferred gene is not completely silenced, a progressive decline in gene expression is often observed. Position effect variegation (PEV) and silencing mechanisms may act on a transferred globin gene residing in chromatin outside of the normal globin locus during the important terminal phases of erythroblast development when globin transcripts normally

accumulate rapidly despite heterochromatization and shutdown of the rest of the genome. The attached table discloses the correcting oligonucleotide base sequences for the beta globin oligonucleotides of the invention.

Table 12
<u>Beta Globin Mutations and Genome-Correcting Oligos</u>

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Sickle Cell Anemia GLU-7-VAL GAG to GTG	TCTGACACAACTGTGTTCACTAGCAACCTCAAACAGACACCA TGGTGCACCTGACTCCTG**<u>A</u>**GGAGAAGTCTGCCGTTACTGCC CTGTGGGGCAAGGTGAACGTGGATGAAGTTGGTGGTGA	357
	TCACCACCAACTTCATCCACGTTCACCTTGCCCCACAGGGCA GTAACGGCAGACTTCTCC**<u>T</u>**CAGGAGTCAGGTGCACCATGGT GTCTGTTTGAGGTTGCTAGTGAACACAGTTGTGTCAGA	358
	GACTCCTG**<u>A</u>**GGAGAAGT	359
	ACTTCTCC**<u>T</u>**CAGGAGTC	360
Thalassaemia Beta MET-0-ARG ATG to AGG	CTATTGCTTACATTTGCTTCTGACACAACTGTGTTCACTAGCA ACCTCAAACAGACACCA**<u>T</u>**GGTGCACCTGACTCCTGAGGAGA AGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGT	361
	ACGTTCACCTTGCCCCACAGGGCAGTAACGGCAGACTTCTC CTCAGGAGTCAGGTGCACC**<u>A</u>**TGGTGTCTGTTTGAGGTTGCT AGTGAACACAGTTGTGTCAGAAGCAAATGTAAGCAATAG	362
	AGACACCA**<u>T</u>**GGTGCACC	363
	GGTGCACC**<u>A</u>**TGGTGTCT	364
Thalassaemia Beta MET-0-ILE ATG to ATA	TATTGCTTACATTTGCTTCTGACACAACTGTGTTCACTAGCAA CCTCAAACAGACACCAT**<u>G</u>**GTGCACCTGACTCCTGAGGAGAA GTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGTG	365
	CACGTTCACCTTGCCCCACAGGGCAGTAACGGCAGACTTCT CCTCAGGAGTCAGGTGCAC**<u>C</u>**ATGGTGTCTGTTTGAGGTTGC TAGTGAACACAGTTGTGTCAGAAGCAAATGTAAGCAATA	366
	GACACCAT**<u>G</u>**GTGCACCT	367
	AGGTGCAC**<u>C</u>**ATGGTGTC	368
Thalassaemia Beta MET-0-ILE ATG to ATT	TATTGCTTACATTTGCTTCTGACACAACTGTGTTCACTAGCAA CCTCAAACAGACACCAT**<u>G</u>**GTGCACCTGACTCCTGAGGA[illegible]A GTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGTG	369

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CACGTTCACCTTGCCCCACAGGGCAGTAACGGCAGACTTCT CCTCAGGAGTCAGGTGCAC**C**ATGGTGTCTGTTTGAGGTTGC TAGTGAACACAGTTGTGTCAGAAGCAAATGTAAGCAATA	370
	GACACCATG**G**GTGCACCT	371
	AGGTGCAC**C**ATGGTGTC	372
Thalassaemia Beta MET-0-LYS ATG to AAG	CTATTGCTTACATTTGCTTCTGACACAACTGTGTTCACTAGCA ACCTCAAACAGACACCA**T**GGTGCACCTGACTCCTGAGGAGA AGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGT	373
	ACGTTCACCTTGCCCCACAGGGCAGTAACGGCAGACTTCTC CTCAGGAGTCAGGTGCACC**A**TGGTGTCTGTTTGAGGTTGCT AGTGAACACAGTTGTGTCAGAAGCAAATGTAAGCAATAG	374
	AGACACCA**T**GGTGCACC	375
	GGTGCACC**A**TGGTGTCT	376
Thalassaemia Beta MET-0-THR ATG to ACG	CTATTGCTTACATTTGCTTCTGACACAACTGTGTTCACTAGCA ACCTCAAACAGACACCA**T**GGTGCACCTGACTCCTGAGGAGA AGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGT	377
	ACGTTCACCTTGCCCCACAGGGCAGTAACGGCAGACTTCTC CTCAGGAGTCAGGTGCACC**A**TGGTGTCTGTTTGAGGTTGCT AGTGAACACAGTTGTGTCAGAAGCAAATGTAAGCAATAG	378
	AGACACCA**T**GGTGCACC	379
	GGTGCACC**A**TGGTGTCT	380
Thalassaemia Beta MET-0-VAL ATG to GTG	TCTATTGCTTACATTTGCTTCTGACACAACTGTGTTCACTAGC AACCTCAAACAGACACC**A**TGGTGCACCTGACTCCTGAGGAG AAGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACG	381
	CGTTCACCTTGCCCCACAGGGCAGTAACGGCAGACTTCTCC TCAGGAGTCAGGTGCACCA**T**GGTGTCTGTTTGAGGTTGCTAG TGAACACAGTTGTGTCAGAAGCAAATGTAAGCAATAGA	382
	CAGACACC**A**TGGTGCAC	383
	GTGCACCA**T**GGTGTCTG	384
Thalassaemia Beta TRP-16-Term TGG to TGA	TCAAACAGACACCATGGTGCACCTGACTCCTGAGGAGAAGT CTGCCGTTACTGCCCTGTG**G**GGCAAGGTGAACGTGGATGAA GTTGGTGGTGAGGCCCTGGGCAGGTTGGTATCAAGGTTA	385
	TAACCTTGATACCAACCTGCCCAGGGCCTCACCACCAACTTC ATCCACGTTCACCTTGCC**C**CACAGGGCAGTAACGGCAGACT TCTCCTCAGGAGTCAGGTGCACCATGGTGTCTGTTTGA	386

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GCCCTGTG**G**GGCAAGGT	387
	ACCTTGCCC**C**CACAGGGC	388
Thalassaemia Beta TRP-16-Term TGG to TAG	CTCAAACAGACACCATGGTGCACCTGACTCCTGAGGAGAAG TCTGCCGTTACTGCCCTGT**G**GGGCAAGGTGAACGTGGATGA AGTTGGTGGTGAGGCCCTGGGCAGGTTGGTATCAAGGTT	389
	AACCTTGATACCAACCTGCCCAGGGCCTCACCACCAACTTCA TCCACGTTCACCTTGCCC**C**ACAGGGCAGTAACGGCAGACTT CTCCTCAGGAGTCAGGTGCACCATGGTGTCTGTTTGAG	390
	TGCCCTGT**G**GGGCAAGG	391
	CCTTGCCC**C**ACAGGGCA	392
Thalassaemia Beta LYS-18-Term AAG to TAG	ACAGACACCATGGTGCACCTGACTCCTGAGGAGAAGTCTGC CGTTACTGCCCTGTGGGGC**A**AGGTGAACGTGGATGAAGTTG GTGGTGAGGCCCTGGGCAGGTTGGTATCAAGGTTACAAG	393
	CTTGTAACCTTGATACCAACCTGCCCAGGGCCTCACCACCAA CTTCATCCACGTTCACCT**T**GCCCCACAGGGCAGTAACGGCA GACTTCTCCTCAGGAGTCAGGTGCACCATGGTGTCTGT	394
	TGTGGGGC**A**AGGTGAAC	395
	GTTCACCT**T**GCCCCACA	396
Thalassaemia Beta ASN-20-SER AAC to AGC	CCATGGTGCACCTGACTCCTGAGGAGAAGTCTGCCGTTACT GCCCTGTGGGGCAAGGTGA**A**CGTGGATGAAGTTGGTGGTGA GGCCCTGGGCAGGTTGGTATCAAGGTTACAAGACAGGTT	397
	AACCTGTCTTGTAACCTTGATACCAACCTGCCCAGGGCCTCA CCACCAACTTCATCCACG**T**TCACCTTGCCCCACAGGGCAGTA ACGGCAGACTTCTCCTCAGGAGTCAGGTGCACCATGG	398
	CAAGGTGA**A**CGTGGATG	399
	CATCCACG**T**TCACCTTG	400
Thalassaemia Beta GLU-23-ALA GAA to GCA	ACCTGACTCCTGAGGAGAAGTCTGCCGTTACTGCCCTGTGG GGCAAGGTGAACGTGGATG**A**AGTTGGTGGTGAGGCCCTGG GCAGGTTGGTATCAAGGTTACAAGACAGGTTTAAGGAGAC	401
	GTCTCCTTAAACCTGTCTTGTAACCTTGATACCAACCTGCCC AGGGCCTCACCACCAACT**T**CATCCACGTTCACCTTGCCCCAC AGGGCAGTAACGGCAGACTTCTCCTCAGGAGTCAGGT	402
	CGTGGATG**A**AGTTGGTG	403
	CACCAACT**T**CATCCACG	404

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Thalassaemia Beta GLU-23-term GAA to TAA	CACCTGACTCCTGAGGAGAAGTCTGCCGTTACTGCCCTGTG GGGCAAGGTGAACGTGGAT**G**AAGTTGGTGGTGAGGCCCTG GGCAGGTTGGTATCAAGGTTACAAGACAGGTTTAAGGAGA	405
	TCTCCTTAAACCTGTCTTGTAACCTTGATACCAACCTGCCCA GGGCCTCACCACCAACTT**C**ATCCACGTTCACCTTGCCCCACA GGGCAGTAACGGCAGACTTCTCCTCAGGAGTCAGGTG	406
	ACGTGGAT**G**AAGTTGGT	407
	ACCAACTT**C**ATCCACGT	408
Thalassaemia Beta GLU-27-LYS GAG to AAG	GAGGAGAAGACTGCTGTCAATGCCCTGTGGGGCAAAGTGAA CGTGGATGCAGTTGGTGGT**G**AGGCCCTGGGCAGGTTGGTAT CAAGGTTATAAGAGAGGCTCAAGGAGGCAAATGGAAACT	409
	AGTTTCCATTTGCCTCCTTGAGCCTCTCTTATAACCTTGATAC CAACCTGCCCAGGGCCT**C**ACCACCAACTGCATCCACGTTCA CTTTGCCCCACAGGGCATTGACAGCAGTCTTCTCCTC	410
	TTGGTGGT**G**AGGCCCTG	411
	CAGGGCCT**C**ACCACCAA	412
Thalassaemia Beta GLU-27-Term GAG to TAG	GAGGAGAAGACTGCTGTCAATGCCCTGTGGGGCAAAGTGAA CGTGGATGCAGTTGGTGGT**G**AGGCCCTGGGCAGGTTGGTAT CAAGGTTATAAGAGAGGCTCAAGGAGGCAAATGGAAACT	413
	AGTTTCCATTTGCCTCCTTGAGCCTCTCTTATAACCTTGATAC CAACCTGCCCAGGGCCT**C**ACCACCAACTGCATCCACGTTCA CTTTGCCCCACAGGGCATTGACAGCAGTCTTCTCCTC	414
	TTGGTGGT**G**AGGCCCTG	415
	CAGGGCCT**C**ACCACCAA	416
Thalassaemia Beta ALA-28-SER GCC to TCC	GAGAAGACTGCTGTCAATGCCCTGTGGGGCAAAGTGAACGT GGATGCAGTTGGTGGTGAG**G**CCCTGGGCAGGTTGGTATCAA GGTTATAAGAGAGGCTCAAGGAGGCAAATGGAAACTGGG	417
	CCCAGTTTCCATTTGCCTCCTTGAGCCTCTCTTATAACCTTGA TACCAACCTGCCCAGGG**C**CTCACCACCAACTGCATCCACGT TCACTTTGCCCCACAGGGCATTGACAGCAGTCTTCTC	418
	GTGGTGAG**G**CCCTGGGC	419
	GCCCAGGG**C**CTCACCAC	420

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Thalassaemia Beta ARG-31-THR AGG to ACG	CTGTCAATGCCCTGTGGGGCAAAGTGAACGTGGATGCAGTTGGTGGTGAGGCCCTGGGCA**G**GTTGGTATCAAGGTTATAAGAGAGGCTCAAGGAGGCAAATGGAAACTGGGCATGTGTAGA	421
	TCTACACATGCCCAGTTTCCATTTGCCTCCTTGAGCCTCTCTTATAACCTTGATACCAAC**C**TGCCCAGGGCCTCACCACCAACTGCATCCACGTTCACTTTGCCCCACAGGGCATTGACAG	422
	CCTGGGCA**G**GTTGGTAT	423
	ATACCAAC**C**TGCCCAGG	424
Thalassaemia Beta Leu-33-GLN CTG to CAG	TGGGTTTCTGATAGGCACTGACTCTCTGTCCCTTGGGCTGTTTTCCTACCCTCAGATTAC**T**GGTGGTCTACCCTTGGACCCAGAGGTTCTTTGAGTCCTTTGGGGATCTGTCCTCTCCTGA	425
	TCAGGAGAGGACAGATCCCCAAAGGACTCAAAGAACCTCTGGGTCCAAGGGTAGACCACC**A**GTAATCTGAGGGTAGGAAAACAGCCCAAGGGACAGAGAGTCAGTGCCTATCAGAAACCCA	426
	CAGATTAC**T**GGTGGTCT	427
	AGACCACC**A**GTAATCTG	428
Thalassaemia Beta TYR-36-Term TAC to TAA	ATAGGCACTGACTCTCTGTCCCTTGGGCTGTTTTCCTACCCTCAGATTACTGGTGGTCTA**C**CCTTGGACCCAGAGGTTCTTTGAGTCCTTTGGGGATCTGTCCTCTCCTGATGCTGTTATG	429
	CATAACAGCATCAGGAGAGGACAGATCCCCAAAGGACTCAAAGAACCTCTGGGTCCAAGG**G**TAGACCACCAGTAATCTGAGGGTAGGAAAACAGCCCAAGGGACAGAGAGTCAGTGCCTAT	430
	GTGGTCTA**C**CCTTGGAC	431
	GTCCAAGG**G**TAGACCAC	432
Thalassaemia Beta TRP-38-Term TGG to TGA	ACTGACTCTCTGTCCCTTGGGCTGTTTTCCTACCCTCAGATTACTGGTGGTCTACCCTTG**G**ACCCAGAGGTTCTTTGAGTCCTTTGGGGATCTGTCCTCTCCTGATGCTGTTATGGGCAAC	433
	GTTGCCCATAACAGCATCAGGAGAGGACAGATCCCCAAAGGACTCAAAGAACCTCTGGGT**C**CAAGGGTAGACCACCAGTAATCTGAGGGTAGGAAAACAGCCCAAGGGACAGAGAGTCAGT	434
	TACCCTTG**G**ACCCAGAG	435
	CTCTGGGT**C**CAAGGGTA	436
Thalassaemia Beta TRP-38-Term TGG to TAG	CACTGACTCTCTGTCCCTTGGGCTGTTTTCCTACCCTCAGATTACTGGTGGTCTACCCTT**G**GACCCAGAGGTTCTTTGAGTCCTTTGGGGATCTGTCCTCTCCTGATGCTGTTATGGGCAA	437

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TTGCCCATAACAGCATCAGGAGAGGACAGATCCCCAAAGGA CTCAAAGAACCTCTGGGTC**C**AAGGGTAGACCACCAGTAATCT GAGGGTAGGAAAACAGCCCAAGGGACAGAGAGTCAGTG	438
	CTACCCTT**G**GACCCAGA	439
	TCTGGGTC**C**AAGGGTAG	440
Thalassaemia Beta GLN-40-Term CAG-TAG	ACTCTCTGTCCCTTGGGCTGTTTTCCTACCCTCAGATTACTG GTGGTCTACCCTTGGACC**C**AGAGGTTCTTTGAGTCCTTTGGG GATCTGTCCTCTCCTGATGCTGTTATGGGCAACCCTA	441
	TAGGGTTGCCCATAACAGCATCAGGAGAGGACAGATCCCCA AAGGACTCAAAGAACCTCT**G**GGTCCAAGGGTAGACCACCAG TAATCTGAGGGTAGGAAAACAGCCCAAGGGACAGAGAGT	442
	CTTGGACC**C**AGAGGTTC	443
	GAACCTCT**G**GGTCCAAG	444
Thalassaemia Beta GLU-44-Term GAG to TAG	TTGGGCTGTTTTCCTACCCTCAGATTACTGGTGGTCTACCCT TGGACCCAGAGGTTCTTT**G**AGTCCTTTGGGGATCTGTCCTCT CCTGATGCTGTTATGGGCAACCCTAAGGTGAAGGCTC	445
	GAGCCTTCACCTTAGGGTTGCCCATAACAGCATCAGGAGAG GACAGATCCCCAAAGGACT**C**AAAGAACCTCTGGGTCCAAGG GTAGACCACCAGTAATCTGAGGGTAGGAAAACAGCCCAA	446
	GGTTCTTT**G**AGTCCTTT	447
	AAAGGACT**C**AAAGAACC	448
Thalassaemia Beta LYS-62-Term AAG to TAG	TTCTTTGAGTCCTTTGGGGATCTGTCCTCTCCTGATGCTGTTA TGGGCAACCCTAAGGTG**A**AGGCTCATGGCAAGAAGGTGCTA GGTGCCTTTAGTGATGGCCTGGCTCACCTGGACAACC	449
	GGTTGTCCAGGTGAGCCAGGCCATCACTAAAGGCACCTAGC ACCTTCTTGCCATGAGCCT**T**CACCTTAGGGTTGCCCATAACA GCATCAGGAGAGGACAGATCCCCAAAGGACTCAAAGAA	450
	CTAAGGTG**A**AGGCTCAT	451
	ATGAGCCT**T**CACCTTAG	452
Thalassaemia Beta SER-73-ARG AGT to AGA	TGCTGTTATGGGCAACCCTAAGGTGAAGGCTCATGGCAAGA AGGTGCTAGGTGCCTTTAG**T**GATGGCCTGGCTCACCTGGAC AACCTCAAGGGCACTTTTTCTCAGCTGAGTGAGCTGCAC	453
	GTGCAGCTCACTCAGCTGAGAAAAAGTGCCCTTGAGGTTGTC CAGGTGAGCCAGGCCATC**A**CTAAAGGCACCTAGCACCTTCT TGCCATGAGCCTTCACCTTAGGGTTGCCCATAACAGCA	454

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GCCTTTAG**T**GATGGCCT	455
	AGGCCATC**A**CTAAAGGC	456
Haemolytic Anaemia GLY-75-VAL GGC to GTC	TTATGGGCAACCCTAAGGTGAAGGCTCATGGCAAGAAGGTG CTAGGTGCCTTTAGTGATG**G**CCTGGCTCACCTGGACAACCT CAAGGGCACTTTTTCTCAGCTGAGTGAGCTGCACTGTGA	457
	TCACAGTGCAGCTCACTCAGCTGAGAAAAAGTGCCCTTGAG GTTGTCCAGGTGAGCCAGG**C**CATCACTAAAGGCACCTAGCA CCTTCTTGCCATGAGCCTTCACCTTAGGGTTGCCCATAA	458
	TAGTGATG**G**CCTGGCTC	459
	GAGCCAGG**C**CATCACTA	460
Thalassaemia Beta GLU-91-Term GAG to TAG	GCCTTTAGTGATGGCCTGGCTCACCTGGACAACCTCAAGGG CACCTTTGCCACACTGAGT**G**AGCTGCACTGTGACAAGCTGC ACGTGGATCCTGAGAACTTCAGGGTGAGTCTATGGGACC	461
	GGTCCCATAGACTCACCCTGAAGTTCTCAGGATCCACGTGCA GCTTGTCACAGTGCAGCT**C**ACTCAGTGTGGCAAAGGTGCCC TTGAGGTTGTCCAGGTGAGCCAGGCCATCACTAAAGGC	462
	CACTGAGT**G**AGCTGCAC	463
	GTGCAGCT**C**ACTCAGTG	464
Thalassaemia Beta VAL-99-MET GTG to ATG	CTGGACAACCTCAAGGGCACTTTTTCTCAGCTGAGTGAGCTG CACTGTGACAAGCTGCAC**G**TGGATCCTGAGAACTTCAGGGT GAGTCCAGGAGATGCTTCACTTTTCTCTTTTTACTTTC	465
	GAAAGTAAAAAGAGAAAAGTGAAGCATCTCCTGGACTCACCC TGAAGTTCTCAGGATCCA**C**GTGCAGCTTGTCACAGTGCAGCT CACTCAGCTGAGAAAAAGTGCCCTTGAGGTTGTCCAG	466
	AGCTGCAC**G**TGGATCCT	467
	AGGATCCA**C**GTGCAGCT	468
Thalassaemia Beta LEU-111-PRO CTG-CCG	CCCTTTTGCTAATCATGTTCATACCTCTTATCTTCCTCCCACA GCTCCTGGGCAACGTGC**T**GGTCTGTGTGCTGGCCCATCACT TTGGCAAAGAATTCACCCCACCAGTGCAGGCTGCCTA	469
	TAGGCAGCCTGCACTGGTGGGGTGAATTCTTTGCCAAAGTG ATGGGCCAGCACACAGACC**A**GCACGTTGCCCAGGAGCTGTG GGAGGAAGATAAGAGGTATGAACATGATTAGCAAAAGGG	470
	CAACGTGC**T**GGTCTGTG	471
	CACAGACC**A**GCACGTTG	472

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Thalassaemia Beta CYS-113-Term TGT to TGA	GCTAATCATGTTCATACCTCTTATCTTCCTCCCACAGCTCCTG GGCAACGTGCTGGTCTG**T**GTGCTGGCCCATCACTTTGGCAA AGAATTCACCCCACCAGTGCAGGCTGCCTATCAGAAA	473
	TTTCTGATAGGCAGCCTGCACTGGTGGGGTGAATTCTTTGCC AAAGTGATGGGCCAGCAC**A**CAGACCAGCACGTTGCCCAGGA GCTGTGGGAGGAAGATAAGAGGTATGAACATGATTAGC	474
	CTGGTCTG**T**GTGCTGGC	475
	GCCAGCAC**A**CAGACCAG	476
Thalassaemia Beta LEU-115-PRO CTG to CCG	TCATGTTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCA ACGTGCTGGTCTGTGTGC**T**GGCCCATCACTTTGGCAAAGAAT TCACCCCACCAGTGCAGGCTGCCTATCAGAAAGTGGT	477
	ACCACTTTCTGATAGGCAGCCTGCACTGGTGGGGTGAATTCT TTGCCAAAGTGATGGGCC**A**GCACACAGACCAGCACGTTGCC CAGGAGCTGTGGGAGGAAGATAAGAGGTATGAACATGA	478
	CTGTGTGC**T**GGCCCATC	479
	GATGGGCC**A**GCACACAG	480
Thalassaemia Beta ALA-116-ASP GCC to GAC	TGTTCATACCTCTTATCTTCCTCCCACAGCTCCTGGGCAACG TGCTGGTCTGTGTGCTGG**C**CCATCACTTTGGCAAAGAATTCA CCCCACCAGTGCAGGCTGCCTATCAGAAAGTGGTGGC	481
	GCCACCACTTTCTGATAGGCAGCCTGCACTGGTGGGGTGAA TTCTTTGCCAAAGTGATGG**G**CCAGCACACAGACCAGCACGTT GCCCAGGAGCTGTGGGAGGAAGATAAGAGGTATGAACA	482
	TGTGCTGG**C**CCATCACT	483
	AGTGATGG**G**CCAGCACA	484
Thalassaemia Beta GLU-122-Term GAA to TAA	TTCCTCCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCT GGCCCATCACTTTGGCAAA**G**AATTCACCCCACCAGTGCAGG CTGCCTATCAGAAAGTGGTGGCTGGTGTGGCTAATGCCC	485
	GGGCATTAGCCACACCAGCCACCACTTTCTGATAGGCAGCC TGCACTGGTGGGGTGAATT**C**TTTGCCAAAGTGATGGGCCAG CACACAGACCAGCACGTTGCCCAGGAGCTGTGGGAGGAA	486
	TTGGCAAA**G**AATTCACC	487
	GGTGAATT**C**TTTGCCAA	488
Thalassaemia Beta GLN-128-PRO CAG to CCG	GCAACGTGCTGGTCTGTGTGCTGGCCCATCACTTTGGCAAA GAATTCACCCCACCAGTGC**A**GGCTGCCTATCAGAAAGTGGT GGCTGGTGTGGCTAATGCCCTGGCCCACAAGTATCACTA	489

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TAGTGATACTTGTGGGCCAGGGCATTAGCCACACCAGCCAC CACTTTCTGATAGGCAGCC**T**GCACTGGTGGGGTGAATTCTTT GCCAAAGTGATGGGCCAGCACACAGACCAGCACGTTGC	490
	ACCAGTGC**A**GGCTGCCT	491
	AGGCAGCC**T**GCACTGGT	492
Thalassaemia Beta GLN-128-Term CAG to TAG	GGCAACGTGCTGGTCTGTGTGCTGGCCCATCACTTTGGCAA AGAATTCACCCCACCAGTG**C**AGGCTGCCTATCAGAAAGTGGT GGCTGGTGTGGCTAATGCCCTGGCCCACAAGTATCACT	493
	AGTGATACTTGTGGGCCAGGGCATTAGCCACACCAGCCACC ACTTTCTGATAGGCAGCCT**G**CACTGGTGGGGTGAATTCTTTG CCAAAGTGATGGGCCAGCACACAGACCAGCACGTTGCC	494
	CACCAGTG**C**AGGCTGCC	495
	GGCAGCCT**G**CACTGGTG	496
Thalassaemia Beta GLN-132-LYS CAG to AAG	GTCTGTGTGCTGGCCCATCACTTTGGCAAAGAATTCACCCCA CCAGTGCAGGCTGCCTAT**C**AGAAAGTGGTGGCTGGTGTGGC TAATGCCCTGGCCCACAAGTATCACTAAGCTCGCTTTC	497
	GAAAGCGAGCTTAGTGATACTTGTGGGCCAGGGCATTAGCC ACACCAGCCACCACTTTCT**G**ATAGGCAGCCTGCACTGGTGG GGTGAATTCTTTGCCAAAGTGATGGGCCAGCACACAGAC	498
	CTGCCTAT**C**AGAAAGTG	499
	CACTTTCT**G**ATAGGCAG	500

EXAMPLE 7

Retinoblastoma

Retinoblastoma (RB) is an embryonic neoplasm of retinal origin. It almost always presents in early childhood and is often bilateral. The risk of osteogenic sarcoma is increased 500-fold in bilateral retinoblastoma patients, the bone malignancy being at sites removed from those exposed to radiation treatment of the eye tumor.

The retinoblastoma susceptibility gene (pRB; pRb) plays a pivotal role in the regulation of the cell cycle. pRB restrains cell cycle progression by maintaining a checkpoint in late G_1 that controls commitment of cells to enter S phase. The critical role that pRB plays in cell cycle regulation explains its

status as archetypal tumor suppressor: loss of pRB function results in an inability to maintain control of the G_1 checkpoint; unchecked progression through the cell cycle is, in turn, a hallmark of neoplasia.

Blanquet *et al.*, *Hum. Molec. Genet.* 4: 383-388 (1995) performed a mutation survey of the RB1 gene in 232 patients with hereditary or nonhereditary retinoblastoma. They systematically explored all 27 exons and flanking sequences, as well as the promoter. All types of point mutations were represented and found to be unequally distributed along the RB1 gene sequence. In the population studied, exons 3, 8, 18, and 19 were preferentially altered. The attached table discloses the correcting oligonucleotide base sequences for the retinoblastoma oligonucleotides of the invention.

Table 13
pRB Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Retinoblastoma Trp99Term TGG-TAG	AATATTTGATCTTTATTTTTTGTTCCCAGGGAGGTTATATTCAAAAGAAAAAGGAACTGT**G**GGGAATCTGTATCTTTATTGCAGCAGTTGACCTAGATGAGATGTCGTTCACTTTTACTGA	501
	TCAGTAAAAGTGAACGACATCTCATCTAGGTCAACTGCTGCAATAAAGATACAGATTCCC**C**ACAGTTCCTTTTTCTTTTGAATATAACCTCCCTGGGAACAAAAAATAAAGATCAAATATT	502
	GGAACTGT**G**GGGAATCT	503
	AGATTCCC**C**ACAGTTCC	504
Retinoblastoma Glu137Asp GAA-GAT	ATTTACTTTTTTCTATTCTTTCCTTTGTAGTGTCCATAAATTCTTTAACTTACTAAAAGA**A**ATTGATACCAGTACCAAAGTTGATAATGCTATGTCAAGACTGTTGAAGAAGTATGATGTA	505
	TACATCATACTTCTTCAACAGTCTTGACATAGCATTATCAACTTTGGTACTGGTATCAAT**T**TCTTTTAGTAAGTTAAAGAATTTATGGACACTACAAAGGAAAGAATAGAAAAAAGTAAAT	506
	CTAAAAGA**A**ATTGATAC	507
	GTATCAAT**T**TCTTTTAG	508
Retinoblastoma Glu137Term GAA-TAA	TGATTTACTTTTTTCTATTCTTTCCTTTGTAGTGTCCATAAATTCTTTAACTTACTAAAA**G**AAATTGATACCAGTACCAAAGTTGATAATGCTATGTCAAGACTGTTGAAGAAGTATGATG	509

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CATCATACTTCTTCAACAGTCTTGACATAGCATTATCAACTTT GGTACTGGTATCAATTT**C**TTTTAGTAAGTTAAAGAATTTATGG ACACTACAAAGGAAAGAATAGAAAAAAGTAAATCA	510
	TACTAAAA**G**AAATTGAT	511
	ATCAATTT**C**TTTTAGTA	512
Retinoblastoma Gln176Term CAA-TAA	AAAATGTTAAAAAGTCATAATGTTTTTCTTTTCAGGACATGTGA ACTTATATATTTGACA**C**AACCCAGCAGTTCGTAAGTAGTTCAC AGAATGTTATTTTTCACTTAAAAAAAAAGATTTT	513
	AAAATCTTTTTTTTTAAGTGAAAAATAACATTCTGTGAACTACT TACGAACTGCTGGGTT**G**TGTCAAATATATAAGTTCACATGTCC TGAAAAGAAAAACATTATGACTTTTTAACATTTT	514
	ATTTGACA**C**AACCCAGC	515
	GCTGGGTT**G**TGTCAAAT	516
Retinoblastoma Ile185Thr ATA-ACA	TGATACATTTTTCCTGTTTTTTTTTCTGCTTTCTATTTGTTTAATA GGATATCTACTGAAA**T**AAATTCTGCATTGGTGCTAAAAGTTTC TTGGATCACATTTTTATTAGCTAAAGGTAAGTT	517
	AACTTACCTTTAGCTAATAAAAATGTGATCCAAGAAACTTTTA GCACCAATGCAGAATTT**A**TTTCAGTAGATATCCTATTAAACAA ATAGAAAGCAGAAAAAAAACAGGAAAAATGTATCA	518
	TACTGAAA**T**AAATTCTG	519
	CAGAATTT**A**TTTCAGTA	520
Retinoblastoma Gln207Term CAA-TAA	AAAGATCTGAATCTCTAACTTTCTTTAAAAATGTACATTTTTTT TTCAGGGGAAGTATTA**C**AAATGGAAGATGATCTGGTGATTTC ATTTCAGTTAATGCTATGTGTCCTTGACTATTTTA	521
	TAAAATAGTCAAGGACACATAGCATTAACTGAAATGAAATCAC CAGATCATCTTCCATTT**G**TAATACTTCCCCTGAAAAAAAAATG TACATTTTTAAAGAAAGTTAGAGATTCAGATCTTT	522
	AAGTATTA**C**AAATGGAA	523
	TTCCATTT**G**TAATACTT	524
Retinoblastoma Arg251Term CGA to TGA	GTTCTTATCTAATTTACCACTTTTACAGAAACAGCTGTTATACC CATTAATGGTTCACCT**C**GAACACCCAGGCGAGGTCAGAACA GGAGTGCACGGATAGCAAAACAACTAGAAAATGATA	525
	TATCATTTTCTAGTTGTTTTGCTATCCGTGCACTCCTGTTCTG ACCTCGCCTGGGTGTTC**G**AGGTGAACCATTAATGGGTATAAC AGCTGTTTCTGTAAAAGTGGTAAATTAGATAAGAAC	526

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GTTCACCT**C**GAACACCC	527
	GGGTGTTC**G**AGGTGAAC	528
Retinoblastoma Arg255Term CGA to TGA	TTTACCACTTTTACAGAAACAGCTGTTATACCCATTAATGGTTCACCTCGAACACCCAGG**C**GAGGTCAGAACAGGAGTGCACGGATAGCAAAACAACTAGAAAATGATACAAGAATTATTG	529
	CAATAATTCTTGTATCATTTTCTAGTTGTTTTGCTATCCGTGCACTCCTGTTCTGACCTC**G**CCTGGGTGTTCGAGGTGAACCATTAATGGGTATAACAGCTGTTTCTGTAAAAGTGGTAAA	530
	CACCCAGG**C**GAGGTCAG	531
	CTGACCTC**G**CCTGGGTG	532
Retinoblastoma Gln266Term CAA to TAA	ATTAATGGTTCACCTCGAACACCCAGGCGAGGTCAGAACAGGAGTGCACGGATAGCAAAA**C**AACTAGAAAATGATACAAGAATTATTGAAGTTCTCTGTAAAGAACATGAATGTAATATAG	533
	CTATATTACATTCATGTTCTTTACAGAGAACTTCAATAATTCTTGTATCATTTTCTAGTT**G**TTTTGCTATCCGTGCACTCCTGTTCTGACCTCGCCTGGGTGTTCGAGGTGAACCATTAAT	534
	TAGCAAAA**C**AACTAGAA	535
	TTCTAGTT**G**TTTTGCTA	536
Retinoblastoma Arg320Term CGA to TGA	TGACATGTAAAGGATAATTGTCAGTGACTTTTTTCTTTCAAGGTTGAAAATCTTTCTAAA**C**GATACGAAGAAATTTATCTTAAAAATAAAGATCTAGATGCAAGATTATTTTTGGATCATG	537
	CATGATCCAAAAATAATCTTGCATCTAGATCTTTATTTTTAAGATAAATTTCTTCGTATC**G**TTTAGAAAGATTTTCAACCTTGAAAGAAAAAAGTCACTGACAATTATCCTTTACATGTCA	538
	TTTCTAAA**C**GATACGAA	539
	TTCGTATC**G**TTTAGAAA	540
Retinoblastoma Gln354Term CAG to TAG	ACAAATTGTAAATTTTCAGTATGTGAATGACTTCACTTATTGTTATTTAGTTTTGAAACA**C**AGAGAACACCACGAAAAAGTAACCTTGATGAAGAGGTGAATGTAATTCCTCCACACACTC	541
	GAGTGTGTGGAGGAATTACATTCACCTCTTCATCAAGGTTACTTTTTCGTGGTGTTCTCT**G**TGTTTCAAAACTAAATAACAATAAGTGAAGTCATTCACATACTGAAAATTTACAATTTGT	542
	TTGAAACA**C**AGAGAACA	543
	TGTTCTCT**G**TGTTTCAA	544

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Retinoblastoma Arg358Gly CGA to GGA	TTTTCAGTATGTGAATGACTTCACTTATTGTTATTTAGTTTTGA AACACAGAGAACACCA**C**GAAAAAGTAACCTTGATGAAGAGGT GAATGTAATTCCTCCACACACTCCAGTTAGGTATG	545
	CATACCTAACTGGAGTGTGTGGAGGAATTACATTCACCTCTT CATCAAGGTTACTTTTTC**G**TGGTGTTCTCTGTGTTTCAAAACT AAATAACAATAAGTGAAGTCATTCACATACTGAAAA	546
	GAACACCA**C**GAAAAAGT	547
	ACTTTTTC**G**TGGTGTTC	548
Retinoblastoma Arg358Term CGA to TGA	TTTTCAGTATGTGAATGACTTCACTTATTGTTATTTAGTTTTGA AACACAGAGAACACCA**C**GAAAAAGTAACCTTGATGAAGAGGT GAATGTAATTCCTCCACACACTCCAGTTAGGTATG	549
	CATACCTAACTGGAGTGTGTGGAGGAATTACATTCACCTCTT CATCAAGGTTACTTTTTC**G**TGGTGTTCTCTGTGTTTCAAAACT AAATAACAATAAGTGAAGTCATTCACATACTGAAAA	550
	GAACACCA**C**GAAAAAGT	551
	ACTTTTTC**G**TGGTGTTC	552
Retinoblastoma Ser397Term TCA to TAA	CTGTTATGAACACTATCCAACAATTAATGATGATTTTAAATTCA GCAAGTGATCAACCTT**C**AGAAAATCTGATTTCCTATTTTAACG TAAGCCATATATGAAACATTATTTATTGTAATAT	553
	ATATTACAATAAATAATGTTTCATATATGGCTTACGTTAAAATA GGAAATCAGATTTTCT**G**AAGGTTGATCACTTGCTGAATTTAAA ATCATCATTAATTGTTGGATAGTGTTCATAACAG	554
	TCAACCTT**C**AGAAAATC	555
	GATTTTCT**G**AAGGTTGA	556
Retinoblastoma Arg445Term CGA to TGA	TTTCATAATTGTGATTTTCTAAAATAGCAGGCTCTTATTTTTCT TTTTGTTTGTTTGTAG**C**GATACAAACTTGGAGTTCGCTTGTAT TACCGAGTAATGGAATCCATGCTTAAATCAGTAA	557
	TTACTGATTTAAGCATGGATTCCATTACTCGGTAATACAAGCG AACTCCAAGTTTGTATC**G**CTACAAACAAACAAAAAGAAAAATA AGAGCCTGCTATTTTAGAAAATCACAATTATGAAA	558
	GTTTGTAG**C**GATACAAA	559
	TTTGTATC**G**CTACAAAC	560
Retinoblastoma Arg455Term CGA to TGA	GCTCTTATTTTTCTTTTTGTTTGTTTGTAGCGATACAAACTTGG AGTTCGCTTGTATTAC**C**GAGTAATGGAATCCATGCTTAAATCA GTAAGTTAAAAACAATATAAAAAAATTTCAGCCG	561

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CGGCTGAAATTTTTTTATATTGTTTTTAACTTACTGATTTAAGC ATGGATTCCATTACTC**G**GTAATACAAGCGAACTCCAAGTTTGT ATCGCTACAAACAAACAAAAAGAAAAATAAGAGC	562
	TGTATTAC**C**GAGTAATG	563
	CATTACTC**G**GTAATACA	564
Retinoblastoma Arg552Term CGA to TGA	ATCGAAAGTTTTATCAAAGCAGAAGGCAACTTGACAAGAGAA ATGATAAAACATTTAGAA**C**GATGTGAACATCGAATCATGGAAT CCCTTGCATGGCTCTCAGTAAGTAGCTAAATAATTG	565
	CAATTATTTAGCTACTTACTGAGAGCCATGCAAGGGATTCCAT GATTCGATGTTCACATC**G**TTCTAAATGTTTTATCATTTCTCTTG TCAAGTTGCCTTCTGCTTTGATAAAACTTTCGAT	566
	ATTTAGAA**C**GATGTGAA	567
	TTCACATC**G**TTCTAAAT	568
Retinoblastoma Cys553Term TGT to TGA	AAGTTTTATCAAAGCAGAAGGCAACTTGACAAGAGAAATGATA AAACATTTAGAACGATG**T**GAACATCGAATCATGGAATCCCTTG CATGGCTCTCAGTAAGTAGCTAAATAATTGAAGAA	569
	TTCTTCAATTATTTAGCTACTTACTGAGAGCCATGCAAGGGAT TCCATGATTCGATGTTC**A**CATCGTTCTAAATGTTTTATCATTTC TCTTGTCAAGTTGCCTTCTGCTTTGATAAAACTT	570
	GAACGATG**T**GAACATCG	571
	CGATGTTC**A**CATCGTTC	572
Retinoblastoma Glu554Term GAA to TAA	AGTTTTATCAAAGCAGAAGGCAACTTGACAAGAGAAATGATAA AACATTTAGAACGATGT**G**AACATCGAATCATGGAATCCCTTG CATGGCTCTCAGTAAGTAGCTAAATAATTGAAGAAA	573
	TTTCTTCAATTATTTAGCTACTTACTGAGAGCCATGCAAGGGA TTCCATGATTCGATGTT**C**ACATCGTTCTAAATGTTTTATCATTT CTCTTGTCAAGTTGCCTTCTGCTTTGATAAAACT	574
	AACGATGT**G**AACATCGA	575
	TCGATGTT**C**ACATCGTT	576
Retinoblastoma Ser567Leu TCA to TTA	TACCTGGGAAAATTATGCTTACTAATGTGGTTTTAATTTCATC ATGTTTCATATAGGATT**C**ACCTTTATTTGATCTTATTAAACAAT CAAAGGACCGAGAAGGACCAACTGATCACCTTGA	577
	TCAAGGTGATCAGTTGGTCCTTCTCGGTCCTTTGATTGTTTAA TAAGATCAAATAAAGGT**G**AATCCTATATGAAACATGATGAAAT TAAAACCACATTAGTAAGCATAATTTTCCCAGGTA	578

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATAGGATT**C**ACCTTTAT	579
	ATAAAGGT**G**AATCCTAT	580
Retinoblastoma Gln575Term CAA to TAA	AATGTGGTTTTAATTTCATCATGTTTCATATAGGATTCACCTTT ATTTGATCTTATTAAA**C**AATCAAAGGACCGAGAAGGACCAACT GATCACCTTGAATCTGCTTGTCCTCTTAATCTTC	581
	GAAGATTAAGAGGACAAGCAGATTCAAGGTGATCAGTTGGTC CTTCTCGGTCCTTTGATT**G**TTTAATAAGATCAAATAAAGGTGA ATCCTATATGAAACATGATGAAATTAAAACCACATT	582
	TTATTAAA**C**AATCAAAG	583
	CTTTGATT**G**TTTAATAA	584
Retinoblastoma Arg579Term CGA to TGA	ATTTCATCATGTTTCATATAGGATTCACCTTTATTTGATCTTAT TAAACAATCAAAGGAC**C**GAGAAGGACCAACTGATCACCTTGA ATCTGCTTGTCCTCTTAATCTTCCTCTCCAGAATA	585
	TATTCTGGAGAGGAAGATTAAGAGGACAAGCAGATTCAAGGT GATCAGTTGGTCCTTCTC**G**GTCCTTTGATTGTTTAATAAGATC AAATAAAGGTGAATCCTATATGAAACATGATGAAAT	586
	CAAAGGAC**C**GAGAAGGA	587
	TCCTTCTC**G**GTCCTTTG	588
Retinoblastoma Glu580Term GAA to TAA	TCATCATGTTTCATATAGGATTCACCTTTATTTGATCTTATTAA ACAATCAAAGGACCGA**G**AAGGACCAACTGATCACCTTGAATC TGCTTGTCCTCTTAATCTTCCTCTCCAGAATAATC	589
	GATTATTCTGGAGAGGAAGATTAAGAGGACAAGCAGATTCAA GGTGATCAGTTGGTCCTT**C**TCGGTCCTTTGATTGTTTAATAAG ATCAAATAAAGGTGAATCCTATATGAAACATGATGA	590
	AGGACCGA**G**AAGGACCA	591
	TGGTCCTT**C**TCGGTCCT	592
Retinoblastoma Ser634Term TCA to TGA	AGAAAAAAGGTTCAACTACGCGTGTAAATTCTACTGCAAATG CAGAGACACAAGCAACCT**C**AGCCTTCCAGACCCAGAAGCCA TTGAAATCTACCTCTCTTTCACTGTTTTATAAAAAAGG	593
	CCTTTTTTATAAAACAGTGAAAGAGAGGTAGATTTCAATGGCT TCTGGGTCTGGAAGGCT**G**AGGTTGCTTGTGTCTCTGCATTTG CAGTAGAATTTACACGCGTAGTTGAACCTTTTTTCT	594
	AGCAACCT**C**AGCCTTCC	595
	GGAAGGCT**G**AGGTTGCT	596

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Retinoblastoma Ala635Pro GCC to CCC	AAAAAAGGTTCAACTACGCGTGTAAATTCTACTGCAAATGCA GAGACACAAGCAACCTCA**G**CCTTCCAGACCCAGAAGCCATT GAAATCTACCTCTCTTTCACTGTTTTATAAAAAAGGTT	597
	AACCTTTTTTATAAAACAGTGAAAGAGAGGTAGATTTCAATGG CTTCTGGGTCTGGAAGG**C**TGAGGTTGCTTGTGTCTCTGCATT TGCAGTAGAATTTACACGCGTAGTTGAACCTTTTTT	598
	CAACCTCA**G**CCTTCCAG	599
	CTGGAAGG**C**TGAGGTTG	600
Retinoblastoma Gln639Term CAG to TAG	ACTACGCGTGTAAATTCTACTGCAAATGCAGAGACACAAGCA ACCTCAGCCTTCCAGACC**C**AGAAGCCATTGAAATCTACCTCT CTTTCACTGTTTTATAAAAAAGGTTAGTAGATGATTA	601
	TAATCATCTACTAACCTTTTTTATAAAACAGTGAAAGAGAGGT AGATTTCAATGGCTTCT**G**GGTCTGGAAGGCTGAGGTTGCTTG TGTCTCTGCATTTGCAGTAGAATTTACACGCGTAGT	602
	TCCAGACC**C**AGAAGCCA	603
	TGGCTTCT**G**GGTCTGGA	604
Retinoblastoma Leu657Pro CTA to CCA	TTGTAATTCAAAATGAACAGTAAAAATGACTAATTTTTCTTATT CCCACAGTGTATCGGC**T**AGCCTATCTCCGGCTAAATACACTT TGTGAACGCCTTCTGTCTGAGCACCCAGAATTAGA	605
	TCTAATTCTGGGTGCTCAGACAGAAGGCGTTCACAAAGTGTA TTTAGCCGGAGATAGGCT**A**GCCGATACACTGTGGGAATAAG AAAAATTAGTCATTTTTACTGTTCATTTTGAATTACAA	606
	GTATCGGC**T**AGCCTATC	607
	GATAGGCT**A**GCCGATAC	608
Retinoblastoma Arg661Trp CGG to TGG	AATGAACAGTAAAAATGACTAATTTTTCTTATTCCCACAGTGTA TCGGCTAGCCTATCTC**C**GGCTAAATACACTTTGTGAACGCCT TCTGTCTGAGCACCCAGAATTAGAACATATCATCT	609
	AGATGATATGTTCTAATTCTGGGTGCTCAGACAGAAGGCGTT CACAAAGTGTATTTAGCC**G**GAGATAGGCTAGCCGATACACTG TGGGAATAAGAAAAATTAGTCATTTTTACTGTTCATT	610
	CCTATCTC**C**GGCTAAAT	611
	ATTTAGCC**G**GAGATAGG	612
Retinoblastoma Leu662Pro CTA to CCA	AACAGTAAAAATGACTAATTTTTCTTATTCCCACAGTGTATCG GCTAGCCTATCTCCGGC**T**AAATACACTTTGTGAACGCCTTCT GTCTGAGCACCCAGAATTAGAACATATCATCTGGAC	613

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GTCCAGATGATATGTTCTAATTCTGGGTGCTCAGACAGAAGG CGTTCACAAAGTGTATTT**A**GCCGGAGATAGGCTAGCCGATAC ACTGTGGGAATAAGAAAAATTAGTCATTTTTACTGTT	614
	TCTCCGGC**T**AAATACAC	615
	GTGTATTT**A**GCCGGAGA	616
Retinoblastoma Glu675Term GAA to TAA	TATCGGCTAGCCTATCTCCGGCTAAATACACTTTGTGAACGC CTTCTGTCTGAGCACCCA**G**AATTAGAACATATCATCTGGACC CTTTTCCAGCACACCCTGCAGAATGAGTATGAACTCA	617
	TGAGTTCATACTCATTCTGCAGGGTGTGCTGGAAAAGGGTCC AGATGATATGTTCTAATT**C**TGGGTGCTCAGACAGAAGGCGTT CACAAAGTGTATTTAGCCGGAGATAGGCTAGCCGATA	618
	AGCACCCA**G**AATTAGAA	619
	TTCTAATT**C**TGGGTGCT	620
Retinoblastoma Gln685Pro CAG to CCG	TTTGTGAACGCCTTCTGTCTGAGCACCCAGAATTAGAACATA TCATCTGGACCCTTTTCC**A**GCACACCCTGCAGAATGAGTATG AACTCATGAGAGACAGGCATTTGGACCAAGTAAGAAA	621
	TTTCTTACTTGGTCCAAATGCCTGTCTCTCATGAGTTCATACT CATTCTGCAGGGTGTGC**T**GGAAAAGGGTCCAGATGATATGTT CTAATTCTGGGTGCTCAGACAGAAGGCGTTCACAAA	622
	CCTTTTCC**A**GCACACCC	623
	GGGTGTGC**T**GGAAAAGG	624
Retinoblastoma Cys706Tyr TGT to TAT	AAAACCATGTAATAAAATTCTGACTACTTTTACATCAATTTATT TACTAGATTATGATGT**G**TTCCATGTATGGCATATGCAAAGTGA AGAATATAGACCTTAAATTCAAAATCATTGTAAC	625
	GTTACAATGATTTTGAATTTAAGGTCTATATTCTTCACTTTGCA TATGCCATACATGGAA**C**ACATCATAATCTAGTAAATAAATTGA TGTAAAAGTAGTCAGAATTTTATTACATGGTTTT	626
	TATGATGT**G**TTCCATGT	627
	ACATGGAA**C**ACATCATA	628
Retinoblastoma Cys712Arg TGC to CGC	TTCTGACTACTTTTACATCAATTTATTTACTAGATTATGATGTG TTCCATGTATGGCATA**T**GCAAAGTGAAGAATATAGACCTTAAA TTCAAAATCATTGTAACAGCATACAAGGATCTTC	629
	GAAGATCCTTGTATGCTGTTACAATGATTTTGAATTTAAGGTC TATATTCTTCACTTTGCA**A**TATGCCATACATGGAACACATCATA ATCTAGTAAATAAATTGATGTAAAAGTAGTCAGAA	630

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATGGCATA**T**GCAAAGTG	631
	CACTTTGC**A**TATGCCAT	632
Retinoblastoma Tyr728Term TAC to TAA	GTATGGCATATGCAAAGTGAAGAATATAGACCTTAAATTCAAA ATCATTGTAACAGCATA**C**AAGGATCTTCCTCATGCTGTTCAG GAGGTAGGTAATTTTCCATAGTAAGTTTTTTTGATA	633
	TATCAAAAAAACTTACTATGGAAAATTACCTACCTCCTGAACA GCATGAGGAAGATCCTT**G**TATGCTGTTACAATGATTTTGAATT TAAGGTCTATATTCTTCACTTTGCATATGCCATAC	634
	ACAGCATA**C**AAGGATCT	635
	AGATCCTT**G**TATGCTGT	636
Retinoblastoma Glu748Term GAG to TAG	TTTTTTTTTTTTTTTTACTGTTCTTCCTCAGACATTCAAACGTGT TTTGATCAAAGAAGAG**G**AGTATGATTCTATTATAGTATTCTATA ACTCGGTCTTCATGCAGAGACTGAAAACAAATA	637
	TATTTGTTTTCAGTCTCTGCATGAAGACCGAGTTATAGAATAC TATAATAGAATCATACT**C**CTCTTCTTTGATCAAAACACGTTTGA ATGTCTGAGGAAGAACAGTAAAAAAAAAAAAAAAA	638
	AAGAAGAG**G**AGTATGAT	639
	ATCATACT**C**CTCTTCTT	640
Retinoblastoma Gln762Term CAG to TAG	GTTTTGATCAAAGAAGAGGAGTATGATTCTATTATAGTATTCT ATAACTCGGTCTTCATG**C**AGAGACTGAAAACAAATATTTTGCA GTATGCTTCCACCAGGGTAGGTCAAAAGTATCCTT	641
	AAGGATACTTTTGACCTACCCTGGTGGAAGCATACTGCAAAA TATTTGTTTTCAGTCTCT**G**CATGAAGACCGAGTTATAGAATAC TATAATAGAATCATACTCCTCTTCTTTGATCAAAAC	642
	TCTTCATG**C**AGAGACTG	643
	CAGTCTCT**G**CATGAAGA	644
Retinoblastoma Arg787Term CGA-TGA	TAATCTACTTTTTTGTTTTTGCTCTAGCCCCCTACCTTGTCAC CAATACCTCACATTCCT**C**GAAGCCCTTACAAGTTTCCTAGTTC ACCCTTACGGATTCCTGGAGGGAACATCTATATTT	645
	AAATATAGATGTTCCCTCCAGGAATCCGTAAGGGTGAACTAG GAAACTTGTAAGGGCTTC**G**AGGAATGTGAGGTATTGGTGACA AGGTAGGGGGCTAGAGCAAAAACAAAAAAGTAGATTA	646
	ACATTCCT**C**GAAGCCCT	647
	AGGGCTTC**G**AGGAATGT	648

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Retinoblastoma Ser816Term TCA to TGA	CCTTACGGATTCCTGGAGGGAACATCTATATTTCACCCCTGA AGAGTCCATATAAAATTT**C**AGAAGGTCTGCCAACACCAACAA AAATGACTCCAAGATCAAGGTGTGTGTTTTCTCTTTA	649
	TAAAGAGAAAACACACACCTTGATCTTGGAGTCATTTTTGTTG GTGTTGGCAGACCTTCT**G**AAATTTTATATGGACTCTTCAGGG GTGAAATATAGATGTTCCCTCCAGGAATCCGTAAGG	650
	TAAAATTT**C**AGAAGGTC	651
	GACCTTCT**G**AAATTTTA	652

EXAMPLE 8
BRCA1 and BRCA2

Breast cancer is the second major cause of cancer death in American women, with an estimated 44,190 lives lost (290 men and 43,900 women) in the US in 1997. While ovarian cancer accounts for fewer deaths than breast cancer, it still represents 4% of all female cancers. In 1994, two breast cancer susceptibility genes were identified: BRCA1 on chromosome 17 and BRCA2 on chromosome 13. When a woman carries a mutation in either BRCA1 or BRCA2, she is at increased risk of being diagnosed with breast or ovarian cancer at some point in her life.

Ford *et al., Am. J. Hum. Genet.* 62: 676-689 (1998) assessed the contribution of BRCA1 and BRCA2 to inherited breast cancer by linkage and mutation analysis in 237 families, each with at least 4 cases of breast cancer. Families were included without regard to the occurrence of ovarian or other cancers. Overall, disease was linked to BRCA1 in an estimated 52% of families, to BRCA2 in 32% of families, and to neither gene in 16%, suggesting other predisposition genes. The majority (81%) of the breast-ovarian cancer families were due to BRCA1, with most others (14%) due to BRCA2. Conversely, the majority (76%) of families with both male and female breast cancer were due to BRCA2. The largest proportion (67%) of families due to other genes were families with 4 or 5 cases of female breast cancer only.

More than 75% of the reported mutations in the BRCA1 gene result in truncated proteins. Couch *et al., Hum. Mutat.* 8: 8-18, 1996. (1996) reported a total of 254 BRCA1 mutations, 132 (52%) of which were unique. A total of 221 (87%) of all mutations or 107 (81%) of the unique mutations are small deletions, insertions, nonsense point mutations, splice variants, and regulatory mutations that result in

truncation or absence of the BRCA1 protein. A total of 11 disease-associated missense mutations (5 unique) and 21 variants (19 unique) as yet unclassified as missense mutations or polymorphisms had been detected. Thirty-five independent benign polymorphisms had been described. The most common mutations were 185delAG and 5382insC, which accounted for 30 (11.7%) and 26 (10.1%), respectively, of all the mutations.

Most BRCA2 mutations are predicted to result in a truncated protein product. The smallest known cancer-associated deletion removes from the C terminus only 224 of the 3,418 residues constituting BRCA2, suggesting that these terminal amino acids are critical for BRCA2 function. Studies (Spain *et al.*, Proc. Natl. Acad. Sci. 96:13920-13925 (1999)) suggest that such truncations eliminate or interfere with 2 nuclear localization signals that reside within the final 156 residues of BRCA2, suggesting that the vast majority of BRCA2 mutants are nonfunctional because they are not translocated into the nucleus.

The attached table discloses the correcting oligonucleotide base sequences for the BRACA1 and BRACA2 oligonucleotides of the invention.

Table 14
BRCA1 Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Met-1-Ile ATG to ATT	CTGCGCTCAGGAGGCCTTCACCCTCTGCTCTGGGTAAAGTT CATTGGAACAGAAAGAAAT**G**GATTTATCTGCTCTTCGCGTTG AAGAAGTACAAAATGTCATTAATGCTATGCAGAAAATC	653
	GATTTTCTGCATAGCATTAATGACATTTTGTACTTCTTCAACG CGAAGAGCAGATAAATC**C**ATTTCTTTCTGTTCCAATGAACTTT ACCCAGAGCAGAGGGTGAAGGCCTCCTGAGCGCAG	654
	AAAGAAAT**G**GATTTATC	655
	GATAAATC**C**ATTTCTTT	656
Breast Cancer Val-11-Ala GTA to GCA	CTGGGTAAAGTTCATTGGAACAGAAAGAAATGGATTTATCTG CTCTTCGCGTTGAAGAAG**T**ACAAAATGTCATTAATGCTATGCA GAAAATCTTAGAGTGTCCCATCTGTCTGGAGTTGAT	657
	ATCAACTCCAGACAGATGGGACACTCTAAGATTTTCTGCATA GCATTAATGACATTTTGT**A**CTTCTTCAACGCGAAGAGCAGATA AATCCATTTCTTTCTGTTCCAATGAACTTTACCCAG	658
	TGAAGAAG**T**ACAAAATG	659

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CATTTTGT**A**CTTCTTCA	660
Breast Cancer Ile-21-Val ATC to GTC	ATGGATTTATCTGCTCTTCGCGTTGAAGAAGTACAAAATGTCA TTAATGCTATGCAGAAA**A**TCTTAGAGTGTCCCATCTGTCTGG AGTTGATCAAGGAACCTGTCTCCACAAAGTGTGACC	661
	GGTCACACTTTGTGGAGACAGGTTCCTTGATCAACTCCAGAC AGATGGGACACTCTAAGA**T**TTTCTGCATAGCATTAATGACATT TTGTACTTCTTCAACGCGAAGAGCAGATAAATCCAT	662
	TGCAGAAA**A**TCTTAGAG	663
	CTCTAAGA**T**TTTCTGCA	664
Breast Cancer Leu-22-Ser TTA to TCA	ATTTATCTGCTCTTCGCGTTGAAGAAGTACAAAATGTCATTAA TGCTATGCAGAAAATCT**T**AGAGTGTCCCATCTGTCTGGAGTT GATCAAGGAACCTGTCTCCACAAAGTGTGACCACAT	665
	ATGTGGTCACACTTTGTGGAGACAGGTTCCTTGATCAACTCC AGACAGATGGGACACTCT**A**AGATTTTCTGCATAGCATTAATG ACATTTTGTACTTCTTCAACGCGAAGAGCAGATAAAT	666
	GAAAATCT**T**AGAGTGTC	667
	GACACTCT**A**AGATTTTC	668
Breast Cancer Cys-39-Tyr TGT to TAT	AGAAAATCTTAGAGTGTCCCATCTGTCTGGAGTTGATCAAGG AACCTGTCTCCACAAAGT**G**TGACCACATATTTTGCAAATTTTG CATGCTGAAACTTCTCAACCAGAAGAAAGGGCCTTC	669
	GAAGGCCCTTTCTTCTGGTTGAGAAGTTTCAGCATGCAAAAT TTGCAAAATATGTGGTCA**C**ACTTTGTGGAGACAGGTTCCTTG ATCAACTCCAGACAGATGGGACACTCTAAGATTTTCT	670
	CACAAAGT**G**TGACCACA	671
	TGTGGTCA**C**ACTTTGTG	672
Breast Cancer Cys-61-Gly TGT to GGT	CACATATTTTGCAAATTTTGCATGCTGAAACTTCTCAACCAGA AGAAAGGGCCTTCACAG**T**GTCCTTTATGTAAGAATGATATAAC CAAAAGGAGCCTACAAGAAAGTACGAGATTTAGTC	673
	GACTAAATCTCGTACTTTCTTGTAGGCTCCTTTTGGTTATATC ATTCTTACATAAAGGAC**A**CTGTGAAGGCCCTTTCTTCTGGTT GAGAAGTTTCAGCATGCAAAATTTGCAAAATATGTG	674
	CTTCACAG**T**GTCCTTTA	675
	TAAAGGAC**A**CTGTGAAG	676

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Leu-63-Stop TTA to TAA	TTTGCAAATTTTGCATGCTGAAACTTCTCAACCAGAAGAAAGG GCCTTCACAGTGTCCTT**T**ATGTAAGAATGATATAACCAAAAGG AGCCTACAAGAAAGTACGAGATTTAGTCAACTTGT	677
	ACAAGTTGACTAAATCTCGTACTTTCTTGTAGGCTCCTTTTGG TTATATCATTCTTACAT**A**AAGGACACTGTGAAGGCCCTTTCTT CTGGTTGAGAAGTTTCAGCATGCAAAATTTGCAAA	678
	GTGTCCTT**T**ATGTAAGA	679
	TCTTACAT**A**AAGGACAC	680
Breast Cancer Cys-64-Arg TGT to CGT Breast Cancer Cys-64-Gly TGT to GGT	TGCAAATTTTGCATGCTGAAACTTCTCAACCAGAAGAAAGGG CCTTCACAGTGTCCTTTA**T**GTAAGAATGATATAACCAAAAGGA GCCTACAAGAAAGTACGAGATTTAGTCAACTTGTTG	681
	CAACAAGTTGACTAAATCTCGTACTTTCTTGTAGGCTCCTTTT GGTTATATCATTCTTAC**A**TAAAGGACACTGTGAAGGCCCTTTC TTCTGGTTGAGAAGTTTCAGCATGCAAAATTTGCA	682
	GTCCTTTA**T**GTAAGAAT	683
	ATTCTTAC**A**TAAAGGAC	684
Breast Cancer Cys-64-Tyr TGT to TAT	GCAAATTTTGCATGCTGAAACTTCTCAACCAGAAGAAAGGGC CTTCACAGTGTCCTTTAT**G**TAAGAATGATATAACCAAAAGGAG CCTACAAGAAAGTACGAGATTTAGTCAACTTGTTGA	685
	TCAACAAGTTGACTAAATCTCGTACTTTCTTGTAGGCTCCTTT TGGTTATATCATTCTTA**C**ATAAAGGACACTGTGAAGGCCCTTT CTTCTGGTTGAGAAGTTTCAGCATGCAAAATTTGC	686
	TCCTTTAT**G**TAAGAATG	687
	CATTCTTA**C**ATAAAGGA	688
Breast Cancer Gln-74-Stop CAA to TAA	CAGAAGAAAGGGCCTTCACAGTGTCCTTTATGTAAGAATGAT ATAACCAAAAGGAGCCTA**C**AAGAAAGTACGAGATTTAGTCAA CTTGTTGAAGAGCTATTGAAAATCATTTGTGCTTTTC	689
	GAAAAGCACAAATGATTTTCAATAGCTCTTCAACAAGTTGACT AAATCTCGTACTTTCTT**G**TAGGCTCCTTTTGGTTATATCATTCT TACATAAAGGACACTGTGAAGGCCCTTTCTTCTG	690
	GGAGCCTA**C**AAGAAAGT	691
	ACTTTCTT**G**TAGGCTCC	692

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Tyr-105-Cys TAT to TGT	AGCTATTGAAAATCATTTGTGCTTTTCAGCTTGACACAGGTTT GGAGTATGCAAACAGCT**A**TAATTTTGCAAAAAAGGAAAATAAC TCTCCTGAACATCTAAAAGATGAAGTTTCTATCAT	693
	ATGATAGAAACTTCATCTTTTAGATGTTCAGGAGAGTTATTTT CCTTTTTTGCAAAATTA**T**AGCTGTTTGCATACTCCAAACCTGT GTCAAGCTGAAAAGCACAAATGATTTTCAATAGCT	694
	AAACAGCT**A**TAATTTTG	695
	CAAAATTA**T**AGCTGTTT	696
Breast Cancer Asn-158-Tyr AAC to TAC	CTACAGAGTGAACCCGAAAATCCTTCCTTGCAGGAAACCAGT CTCAGTGTCCAACTCTCT**A**ACCTTGGAACTGTGAGAACTCTG AGGACAAAGCAGCGGATACAACCTCAAAAGACGTCTG	697
	CAGACGTCTTTTGAGGTTGTATCCGCTGCTTTGTCCTCAGAG TTCTCACAGTTCCAAGGT**T**AGAGAGTTGGACACTGAGACTGG TTTCCTGCAAGGAAGGATTTTCGGGTTCACTCTGTAG	698
	AACTCTCT**A**ACCTTGGA	699
	TCCAAGGT**T**AGAGAGTT	700
Breast Cancer Gln-169-Stop CAG to TAG	GAAACCAGTCTCAGTGTCCAACTCTCTAACCTTGGAACTGTG AGAACTCTGAGGACAAAG**C**AGCGGATACAACCTCAAAAGAC GTCTGTCTACATTGAATTGGGATCTGATTCTTCTGAAG	701
	CTTCAGAAGAATCAGATCCCAATTCAATGTAGACAGACGTCTT TTGAGGTTGTATCCGCT**G**CTTTGTCCTCAGAGTTCTCACAGT TCCAAGGTTAGAGAGTTGGACACTGAGACTGGTTTC	702
	GGACAAAG**C**AGCGGATA	703
	TATCCGCT**G**CTTTGTCC	704
Breast Cancer Trp-353-Stop TGG to TAG	CTCCCAGCACAGAAAAAAAGGTAGATCTGAATGCTGATCCCC TGTGTGAGAGAAAAGAAT**G**GAATAAGCAGAAACTGCCATGCT CAGAGAATCCTAGAGATACTGAAGATGTTCCTTGGAT	705
	ATCCAAGGAACATCTTCAGTATCTCTAGGATTCTCTGAGCAT GGCAGTTTCTGCTTATTC**C**ATTCTTTTCTCTCACACAGGGGAT CAGCATTCAGATCTACCTTTTTTTCTGTGCTGGGAG	706
	AAAAGAAT**G**GAATAAGC	707
	GCTTATTC**C**ATTCTTTT	708
Breast Cancer Ile-379-Met ATT to ATG	ATGCTCAGAGAATCCTAGAGATACTGAAGATGTTCCTTGGAT AACACTAAATAGCAGCAT**T**CAGAAAGTTAATGAGTGGTTTTCC AGAAGTGATGAACTGTTAGGTTCTGATGACTCACAT	709

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATGTGAGTCATCAGAACCTAACAGTTCATCACTTCTGGAAAAC CACTCATTAACTTTCTG**A**ATGCTGCTATTTAGTGTTATCCAAG GAACATCTTCAGTATCTCTAGGATTCTCTGAGCAT	710
	AGCAGCATT**T**CAGAAAGT	711
	ACTTTCTG**A**ATGCTGCT	712
Breast Cancer Glu-421-Gly GAA to GGA	GGGAGTCTGAATCAAATGCCAAAGTAGCTGATGTATTGGACG TTCTAAATGAGGTAGATG**A**ATATTCTGGTTCTTCAGAGAAAAT AGACTTACTGGCCAGTGATCCTCATGAGGCTTTAAT	713
	ATTAAAGCCTCATGAGGATCACTGGCCAGTAAGTCTATTTTCT CTGAAGAACCAGAATAT**T**CATCTACCTCATTTAGAACGTCCAA TACATCAGCTACTTTGGCATTTGATTCAGACTCCC	714
	GGTAGATG**A**ATATTCTG	715
	CAGAATAT**T**CATCTACC	716
Breast Cancer Phe-461-Leu TTT to CTT	ATATGTAAAAGTGAAAGAGTTCACTCCAAATCAGTAGAGAGTA ATATTGAAGACAAAATA**T**TTGGGAAAACCTATCGGAAGAAGG CAAGCCTCCCCAACTTAAGCCATGTAACTGAAAATC	717
	GATTTTCAGTTACATGGCTTAAGTTGGGGAGGCTTGCCTTCT TCCGATAGGTTTTCCCAA**A**TATTTTGTCTTCAATATTACTCTCT ACTGATTTGGAGTGAACTCTTTCACTTTTACATAT	718
	ACAAAATA**T**TTGGGAAA	719
	TTTCCCAA**A**TATTTTGT	720
Breast Cancer Tyr-465-Leu TAT to GAT	GAAAGAGTTCACTCCAAATCAGTAGAGAGTAATATTGAAGAC AAAATATTTGGGAAAACC**T**ATCGGAAGAAGGCAAGCCTCCCC AACTTAAGCCATGTAACTGAAAATCTAATTATAGGAG	721
	CTCCTATAATTAGATTTTCAGTTACATGGCTTAAGTTGGGGAG GCTTGCCTTCTTCCGAT**A**GGTTTTCCCAAATATTTTGTCTTCA ATATTACTCTCTACTGATTTGGAGTGAACTCTTTC	722
	GGAAAACC**T**ATCGGAAG	723
	CTTCCGAT**A**GGTTTTCC	724
Breast Cancer Gly-484-Stop GGA to TGA	ACCTATCGGAAGAAGGCAAGCCTCCCCAACTTAAGCCATGTA ACTGAAAATCTAATTATA**G**GAGCATTTGTTACTGAGCCACAGA TAATACAAGAGCGTCCCCTCACAAATAAATTAAAGC	725
	GCTTTAATTTATTTGTGAGGGGACGCTCTTGTATTATCTGTGG CTCAGTAACAAATGCTC**C**TATAATTAGATTTTCAGTTACATGG CTTAAGTTGGGGAGGCTTGCCTTCTTCCGATAGGT	726

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TAATTATA**G**GAGCATTT	727
	AAATGCTC**C**TATAATTA	728
Breast Cancer Arg-507-Ile AGA to ATA	TTACTGAGCCACAGATAATACAAGAGCGTCCCCTCACAAATAAATTAAAGCGTAAAAGGA**G**ACCTACATCAGGCCTTCATCCTGAGGATTTTATCAAGAAAGCAGATTTGGCAGTTCAAAA	729
	TTTTGAACTGCCAAATCTGCTTTCTTGATAAAATCCTCAGGATGAAGGCCTGATGTAGGT**C**TCCTTTTACGCTTTAATTTATTTGTGAGGGGACGCTCTTGTATTATCTGTGGCTCAGTAA	730
	TAAAAGGA**G**ACCTACAT	731
	ATGTAGGT**C**TCCTTTTA	732
Breast Cancer Ser-510-Stop TCA to TGA	CACAGATAATACAAGAGCGTCCCCTCACAAATAAATTAAAGCGTAAAAGGAGACCTACAT**C**AGGCCTTCATCCTGAGGATTTTATCAAGAAAGCAGATTTGGCAGTTCAAAAGACTCCTGA	733
	TCAGGAGTCTTTTGAACTGCCAAATCTGCTTTCTTGATAAAATCCTCAGGATGAAGGCCT**G**ATGTAGGTCTCCTTTTACGCTTTAATTTATTTGTGAGGGGACGCTCTTGTATTATCTGTG	734
	ACCTACAT**C**AGGCCTTC	735
	GAAGGCCT**G**ATGTAGGT	736
Breast Cancer Gln-526-Stop CAA to TAA	AGGAGACCTACATCAGGCCTTCATCCTGAGGATTTTATCAAGAAAGCAGATTTGGCAGTT**C**AAAAGACTCCTGAAATGATAAATCAGGGAACTAACCAAACGGAGCAGAATGGTCAAGTGA	737
	TCACTTGACCATTCTGCTCCGTTTGGTTAGTTCCCTGATTTATCATTTCAGGAGTCTTTT**G**AACTGCCAAATCTGCTTTCTTGATAAAATCCTCAGGATGAAGGCCTGATGTAGGTCTCCT	738
	TGGCAGTT**C**AAAAGACT	739
	AGTCTTTT**G**AACTGCCA	740
Breast Cancer Gln-541-Stop CAG to TAG	AGGAGACCTACATCAGGCCTTCATCCTGAGGATTTTATCAAGAAAGCAGATTTGGCAGTT**C**AAAAGACTCCTGAAATGATAAATCAGGGAACTAACCAAACGGAGCAGAATGGTCAAGTGA	741
	TCACTTGACCATTCTGCTCCGTTTGGTTAGTTCCCTGATTTATCATTTCAGGAGTCTTTT**G**AACTGCCAAATCTGCTTTCTTGATAAAATCCTCAGGATGAAGGCCTGATGTAGGTCTCCT	742
	AAACGGAG**C**AGAATGGT	743
	ACCATTCT**G**CTCCGTTT	744

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Gly-552-Val GGT to GTT	TAAATCAGGGAACTAACCAAACGGAGCAGAATGGTCAAGTGA TGAATATTACTAATAGTG**G**TCATGAGAATAAAACAAAAGGTGA TTCTATTCAGAATGAGAAAAATCCTAACCCAATAGA	745
	TCTATTGGGTTAGGATTTTTCTCATTCTGAATAGAATCACCTTT TGTTTTATTCTCATGA**C**CACTATTAGTAATATTCATCACTTGAC CATTCTGCTCCGTTTGGTTAGTTCCCTGATTTA	746
	TAATAGTG**G**TCATGAGA	747
	TCTCATGA**C**CACTATTA	748
Breast Cancer Gln-563-Stop CAG to TAG	GGTCAAGTGATGAATATTACTAATAGTGGTCATGAGAATAAAA CAAAAGGTGATTCTATT**C**AGAATGAGAAAAATCCTAACCCAAT AGAATCACTCGAAAAAGAATCTGCTTTCAAAACGA	749
	TCGTTTTGAAAGCAGATTCTTTTTCGAGTGATTCTATTGGGTT AGGATTTTTCTCATTCT**G**AATAGAATCACCTTTTGTTTTATTCT CATGACCACTATTAGTAATATTCATCACTTGACC	750
	ATTCTATT**C**AGAATGAG	751
	CTCATTCT**G**AATAGAAT	752
Ovarian Cancer Lys-607-Stop AAA to TAA	ATAAGCAGCAGTATAAGCAATATGGAACTCGAATTAAATATCC ACAATTCAAAAGCACCT**A**AAAAGAATAGGCTGAGGAGGAAGT CTTCTACCAGGCATATTCATGCGCTTGAACTAGTAG	753
	CTACTAGTTCAAGCGCATGAATATGCCTGGTAGAAGACTTCC TCCTCAGCCTATTCTTTT**T**AGGTGCTTTTGAATTGTGGATATT TAATTCGAGTTCCATATTGCTTATACTGCTGCTTAT	754
	AAGCACCT**A**AAAAGAAT	755
	ATTCTTTT**T**AGGTGCTT	756
Breast Cancer Leu-639-Stop TTG to TAG	ATATTCATGCGCTTGAACTAGTAGTCAGTAGAAATCTAAGCCC ACCTAATTGTACTGAAT**T**GCAAATTGATAGTTGTTCTAGCAGT GAAGAGATAAAGAAAAAAAAGTACAACCAAATGCC	757
	GGCATTTGGTTGTACTTTTTTTTCTTTATCTCTTCACTGCTAGA ACAACTATCAATTTGC**A**ATTCAGTACAATTAGGTGGGCTTAGA TTTCTACTGACTACTAGTTCAAGCGCATGAATAT	758
	TACTGAAT**T**GCAAATTG	759
	CAATTTGC**A**ATTCAGTA	760
Breast Cancer Asp-693-Asn GAC to AAC	GAACCTGCAACTGGAGCCAAGAAGAGTAACAAGCCAAATGAA CAGACAAGTAAAAGACAT**G**ACAGCGATACTTTCCCAGAGCTG AAGTTAACAAATGCACCTGGTTCTTTTACTAAGTGTT	761

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AACACTTAGTAAAAGAACCAGGTGCATTTGTTAACTTCAGCTC TGGGAAAGTATCGCTGT**C**ATGTCTTTTACTTGTCTGTTCATTT GGCTTGTTACTCTTCTTGGCTCCAGTTGCAGGTTC	762
	AAAGACAT**G**ACAGCGAT	763
	ATCGCTGT**C**ATGTCTTT	764
Ovarian Cancer Glu-720-Stop GAA to TAA	CTGAAGTTAACAAATGCACCTGGTTCTTTTACTAAGTGTTCAA ATACCAGTGAACTTAAA**G**AATTTGTCAATCCTAGCCTTCCAAG AGAAGAAAAAGAAGAGAAACTAGAAACAGTTAAAG	765
	CTTTAACTGTTTCTAGTTTCTCTTCTTTTTCTTCTCTTGGAAGG CTAGGATTGACAAATT**C**TTTAAGTTCACTGGTATTTGAACACT TAGTAAAAGAACCAGGTGCATTTGTTAACTTCAG	766
	AACTTAAA**G**AATTTGTC	767
	GACAAATT**C**TTTAAGTT	768
Breast Cancer Glu-755-Stop GAA to TAA	CTAGAAACAGTTAAAGTGTCTAATAATGCTGAAGACCCCAAA GATCTCATGTTAAGTGGA**G**AAAGGGTTTTGCAAACTGAAAGA TCTGTAGAGAGTAGCAGTATTTCATTGGTACCTGGTA	769
	TACCAGGTACCAATGAAATACTGCTACTCTCTACAGATCTTTC AGTTTGCAAAACCCTTT**C**TCCACTTAACATGAGATCTTTGGGG TCTTCAGCATTATTAGACACTTTAACTGTTTCTAG	770
	TAAGTGGA**G**AAAGGGTT	771
	AACCCTTT**C**TCCACTTA	772
Breast Cancer Ser-770-Stop TCA to TAA	TCATGTTAAGTGGAGAAAGGGTTTTGCAAACTGAAAGATCTG TAGAGAGTAGCAGTATTT**C**ATTGGTACCTGGTACTGATTATG GCACTCAGGAAAGTATCTCGTTACTGGAAGTTAGCAC	773
	GTGCTAACTTCCAGTAACGAGATACTTTCCTGAGTGCCATAA TCAGTACCAGGTACCAAT**G**AAATACTGCTACTCTCTACAGAT CTTTCAGTTTGCAAAACCCTTTCTCCACTTAACATGA	774
	CAGTATTT**C**ATTGGTAC	775
	GTACCAAT**G**AAATACTG	776
Breast Cancer Val-772-Ala GTA to GCA	TAAGTGGAGAAAGGGTTTTGCAAACTGAAAGATCTGTAGAGA GTAGCAGTATTTCATTGG**T**ACCTGGTACTGATTATGGCACTC AGGAAAGTATCTCGTTACTGGAAGTTAGCACTCTAGG	777
	CCTAGAGTGCTAACTTCCAGTAACGAGATACTTTCCTGAGTG CCATAATCAGTACCAGGT**A**CCAATGAAATACTGCTACTCTCTA CAGATCTTTCAGTTTGCAAAACCCTTTCTCCACTTA	778

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TTCATTGG**T**ACCTGGTA	779
	TACCAGGT**A**CCAATGAA	780
Breast Cancer Gln-780-Stop CAG to TAG	ACTGAAAGATCTGTAGAGAGTAGCAGTATTTCATTGGTACCT GGTACTGATTATGGCACT**C**AGGAAAGTATCTCGTTACTGGAA GTTAGCACTCTAGGGAAGGCAAAAACAGAACCAAATA	781
	TATTTGGTTCTGTTTTTGCCTTCCCTAGAGTGCTAACTTCCAG TAACGAGATACTTTCCT**G**AGTGCCATAATCAGTACCAGGTAC CAATGAAATACTGCTACTCTCTACAGATCTTTCAGT	782
	ATGGCACT**C**AGGAAAGT	783
	ACTTTCCT**G**AGTGCCAT	784
Breast Cancer Glu-797-Stop GAA to TAA	TATGGCACTCAGGAAAGTATCTCGTTACTGGAAGTTAGCACT CTAGGGAAGGCAAAAACA**G**AACCAAATAAATGTGTGAGTCAG TGTGCAGCATTTGAAAACCCCAAGGGACTAATTCATG	785
	CATGAATTAGTCCCTTGGGGTTTTCAAATGCTGCACACTGAC TCACACATTTATTTGGTT**C**TGTTTTTGCCTTCCCTAGAGTGCT AACTTCCAGTAACGAGATACTTTCCTGAGTGCCATA	786
	CAAAAACA**G**AACCAAAT	787
	ATTTGGTT**C**TGTTTTTG	788
Breast Cancer Lys-820-Glu AAA to GAA	AAATGTGTGAGTCAGTGTGCAGCATTTGAAAACCCCAAGGGA CTAATTCATGGTTGTTCC**A**AAGATAATAGAAATGACACAGAAG GCTTTAAGTATCCATTGGGACATGAAGTTAACCACA	789
	TGTGGTTAACTTCATGTCCCAATGGATACTTAAAGCCTTCTGT GTCATTTCTATTATCTT**T**GGAACAACCATGAATTAGTCCCTTG GGGTTTTCAAATGCTGCACACTGACTCACACATTT	790
	GTTGTTCC**A**AAGATAAT	791
	ATTATCTT**T**GGAACAAC	792
Breast Cancer Thr-826-Lys ACA to AAA	CAGCATTTGAAAACCCCAAGGGACTAATTCATGGTTGTTCCA AAGATAATAGAAATGACA**C**AGAAGGCTTTAAGTATCCATTGG GACATGAAGTTAACCACAGTCGGGAAACAAGCATAGA	793
	TCTATGCTTGTTTCCCGACTGTGGTTAACTTCATGTCCCAATG GATACTTAAAGCCTTCT**G**TGTCATTTCTATTATCTTTGGAACA ACCATGAATTAGTCCCTTGGGGTTTTCAAATGCTG	794
	AAATGACA**C**AGAAGGCT	795
	AGCCTTCT**G**TGTCATTT	796

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Arg-841-Trp CGG to TGG	GATAATAGAAATGACACAGAAGGCTTTAAGTATCCATTGGGACATGAAGTTAACCACAGT**C**GGGAAACAAGCATAGAAATGGAAGAAAGTGAACTTGATGCTCAGTATTTGCAGAATACAT	797
	ATGTATTCTGCAAATACTGAGCATCAAGTTCACTTTCTTCCATTTCTATGCTTGTTTCCC**G**ACTGTGGTTAACTTCATGTCCCAATGGATACTTAAAGCCTTCTGTGTCATTTCTATTATC	798
	ACCACAGT**C**GGGAAACA	799
	TGTTTCCC**G**ACTGTGGT	800
Breast Cancer Pro-871-Leu CCG to CTG	AACTTGATGCTCAGTATTTGCAGAATACATTCAAGGTTTCAAAGCGCCAGTCATTTGCTC**C**GTTTTCAAATCCAGGAAATGCAGAAGAGGAATGTGCAACATTCTCTGCCCACTCTGGGTC	801
	GACCCAGAGTGGGCAGAGAATGTTGCACATTCCTCTTCTGCATTTCCTGGATTTGAAAAC**G**GAGCAAATGACTGGCGCTTTGAAACCTTGAATGTATTCTGCAAATACTGAGCATCAAGTT	802
	ATTTGCTC**C**GTTTTCAA	803
	TTGAAAAC**G**GAGCAAAT	804
Breast Cancer Leu-892-Ser TTA to TCA	TTTCAAATCCAGGAAATGCAGAAGAGGAATGTGCAACATTCTCTGCCCACTCTGGGTCCT**T**AAAGAAACAAAGTCCAAAAGTCACTTTTGAATGTGAACAAAAGGAAGAAAATCAAGGAAA	805
	TTTCCTTGATTTTCTTCCTTTTGTTCACATTCAAAAGTGACTTTTGGACTTTGTTTCTTT**A**AGGACCCAGAGTGGGCAGAGAATGTTGCACATTCCTCTTCTGCATTTCCTGGATTTGAAA	806
	TGGGTCCT**T**AAAGAAAC	807
	GTTTCTTT**A**AGGACCCA	808
Breast Cancer Glu-908-Stop GAA to TAA	CACTCTGGGTCCTTAAAGAAACAAAGTCCAAAAGTCACTTTTGAATGTGAACAAAAGGAA**G**AAAATCAAGGAAAGAATGAGTCTAATATCAAGCCTGTACAGACAGTTAATATCACTGCAG	809
	CTGCAGTGATATTAACTGTCTGTACAGGCTTGATATTAGACTCATTCTTTCCTTGATTTT**C**TTCCTTTTGTTCACATTCAAAAGTGACTTTTGGACTTTGTTTCTTTAAGGACCCAGAGTG	810
	AAAAGGAA**G**AAAATCAA	811
	TTGATTTT**C**TTCCTTTT	812
Breast Cancer Gly-960-Asp GGC to GAC	ATAATGCCAAATGTAGTATCAAAGGAGGCTCTAGGTTTTGTCTATCATCTCAGTTCAGAG**G**CAACGAAACTGGACTCATTACTCCAAATAAACATGGACTTTTACAAAACCCATATCGTAT	813

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATACGATATGGGTTTTGTAAAAGTCCATGTTTATTTGGAGTAA TGAGTCCAGTTTCGTTG**C**CTCTGAACTGAGATGATAGACAAA ACCTAGAGCCTCCTTTGATACTACATTTGGCATTAT	814
	GTTCAGAG**G**CAACGAAA	815
	TTTCGTTG**C**CTCTGAAC	816
Breast Cancer Met-1008-Ile ATG to ATA	ATTTGTTAAAACTAAATGTAAGAAAAATCTGCTAGAGGAAAAC TTTGAGGAACATTCAAT**G**TCACCTGAAAGAGAAATGGGAAAT GAGAACATTCCAAGTACAGTGAGCACAATTAGCCGT	817
	ACGGCTAATTGTGCTCACTGTACTTGGAATGTTCTCATTTCCC ATTTCTCTTTCAGGTGA**C**ATTGAATGTTCCTCAAAGTTTTCCT CTAGCAGATTTTTCTTACATTTAGTTTTAACAAAT	818
	CATTCAAT**G**TCACCTGA	819
	TCAGGTGA**C**ATTGAATG	820
Breast Cancer Thr-1025-Ile ACA to ATA	ACTTTGAGGAACATTCAATGTCACCTGAAAGAGAAATGGGAA ATGAGAACATTCCAAGTA**C**AGTGAGCACAATTAGCCGTAATA ACATTAGAGAAAATGTTTTTAAAGAAGCCAGCTCAAG	821
	CTTGAGCTGGCTTCTTTAAAAACATTTTCTCTAATGTTATTACG GCTAATTGTGCTCACT**G**TACTTGGAATGTTCTCATTTCCCATT TCTCTTTCAGGTGACATTGAATGTTCCTCAAAGT	822
	TCCAAGTA**C**AGTGAGCA	823
	TGCTCACT**G**TACTTGGA	824
Breast Cancer Glu-1038-Gly GAA to GGA	ACATTCCAAGTACAGTGAGCACAATTAGCCGTAATAACATTAG AGAAAATGTTTTTAAAG**A**AGCCAGCTCAAGCAATATTAATGAA GTAGGTTCCAGTACTAATGAAGTGGGCTCCAGTAT	825
	ATACTGGAGCCCACTTCATTAGTACTGGAACCTACTTCATTAA TATTGCTTGAGCTGGCT**T**CTTTAAAAACATTTTCTCTAATGTTA TTACGGCTAATTGTGCTCACTGTACTTGGAATGT	826
	TTTTAAAG**A**AGCCAGCT	827
	AGCTGGCT**T**CTTTAAAA	828
Breast Cancer Ser-1040-Asn AGC to AAC	CAAGTACAGTGAGCACAATTAGCCGTAATAACATTAGAGAAA ATGTTTTTAAAGAAGCCA**G**CTCAAGCAATATTAATGAAGTAGG TTCCAGTACTAATGAAGTGGGCTCCAGTATTAATGA	829
	TCATTAATACTGGAGCCCACTTCATTAGTACTGGAACCTACTT CATTAATATTGCTTGAG**C**TGGCTTCTTTAAAAACATTTTCTCTA ATGTTATTACGGCTAATTGTGCTCACTGTACTTG	830

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGAAGCCA**G**CTCAAGCA	831
	TGCTTGAG**C**TGGCTTCT	832
Breast Cancer Val-1047-Ala GTA to GCA	GCCGTAATAACATTAGAGAAAATGTTTTTAAAGAAGCCAGCTC AAGCAATATTAATGAAG**T**AGGTTCCAGTACTAATGAAGTGGG CTCCAGTATTAATGAAATAGGTTCCAGTGATGAAAA	833
	TTTTCATCACTGGAACCTATTTCATTAATACTGGAGCCCACTT CATTAGTACTGGAACCT**A**CTTCATTAATATTGCTTGAGCTGGC TTCTTTAAAAACATTTTCTCTAATGTTATTACGGC	834
	TAATGAAG**T**AGGTTCCA	835
	TGGAACCT**A**CTTCATTA	836
Breast Cancer Leu-1080-Stop TTG to TAG	AAATAGGTTCCAGTGATGAAAACATTCAAGCAGAACTAGGTA GAAACAGAGGGCCAAAAT**T**GAATGCTATGCTTAGATTAGGGG TTTTGCAACCTGAGGTCTATAAACAAAGTCTTCCTGG	837
	CCAGGAAGACTTTGTTTATAGACCTCAGGTTGCAAAACCCCT AATCTAAGCATAGCATTC**A**ATTTTGGCCCTCTGTTTCTACCTA GTTCTGCTTGAATGTTTTCATCACTGGAACCTATTT	838
	GCCAAAAT**T**GAATGCTA	839
	TAGCATTC**A**ATTTTGGC	840
Breast Cancer Leu-1086-Stop TTA to TGA	AAAACATTCAAGCAGAACTAGGTAGAAACAGAGGGCCAAAAT TGAATGCTATGCTTAGAT**T**AGGGGTTTTGCAACCTGAGGTCT ATAAACAAAGTCTTCCTGGAAGTAATTGTAAGCATCC	841
	GGATGCTTACAATTACTTCCAGGAAGACTTTGTTTATAGACCT CAGGTTGCAAAACCCCT**A**ATCTAAGCATAGCATTCAATTTTG GCCCTCTGTTTCTACCTAGTTCTGCTTGAATGTTTT	842
	GCTTAGAT**T**AGGGGTTT	843
	AAACCCCT**A**ATCTAAGC	844
Breast Cancer Ser-1130-Stop TCA to TGA	AGCAAGAATATGAAGAAGTAGTTCAGACTGTTAATACAGATTT CTCTCCATATCTGATTT**C**AGATAACTTAGAACAGCCTATGGGA AGTAGTCATGCATCTCAGGTTTGTTCTGAGACACC	845
	GGTGTCTCAGAACAAACCTGAGATGCATGACTACTTCCCATA GGCTGTTCTAAGTTATCT**G**AAATCAGATATGGAGAGAAATCT GTATTAACAGTCTGAACTACTTCTTCATATTCTTGCT	846
	TCTGATTT**C**AGATAACT	847
	AGTTATCT**G**AAATCAGA	848

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Lys-1183-Arg AAA to AGA	CTAGTTTTGCTGAAAATGACATTAAGGAAAGTTCTGCTGTTTTTAGCAAAAGCGTCCAGA**A**AGGAGAGCTTAGCAGGAGTCCTAGCCCTTTCACCCATACACATTTGGCTCAGGGTTACCG	849
	CGGTAACCCTGAGCCAAATGTGTATGGGTGAAAGGGCTAGGACTCCTGCTAAGCTCTCCT**T**TCTGGACGCTTTTGCTAAAAACAGCAGAACTTTCCTTAATGTCATTTTCAGCAAAACTAG	850
	CGTCCAGA**A**AGGAGAGC	851
	GCTCTCCT**T**TCTGGACG	852
Breast Cancer Gln-1200-Stop CAG to TAG	AGCGTCCAGAAAGGAGAGCTTAGCAGGAGTCCTAGCCCTTTCACCCATACACATTTGGCT**C**AGGGTTACCGAAGAGGGGCCAAGAAATTAGAGTCCTCAGAAGAGAACTTATCTAGTGAGG	853
	CCTCACTAGATAAGTTCTCTTCTGAGGACTCTAATTTCTTGGCCCCTCTTCGGTAACCCT**G**AGCCAAATGTGTATGGGTGAAAGGGCTAGGACTCCTGCTAAGCTCTCCTTTCTGGACGCT	854
	ATTTGGCT**C**AGGGTTAC	855
	GTAACCCT**G**AGCCAAAT	856
Breast Cancer Arg-1203-Stop CGA to TGA	AAAGGAGAGCTTAGCAGGAGTCCTAGCCCTTTCACCCATACACATTTGGCTCAGGGTTAC**C**GAAGAGGGGCCAAGAAATTAGAGTCCTCAGAAGAGAACTTATCTAGTGAGGATGAAGAGC	857
	GCTCTTCATCCTCACTAGATAAGTTCTCTTCTGAGGACTCTAATTTCTTGGCCCCTCTTC**G**GTAACCCTGAGCCAAATGTGTATGGGTGAAAGGGCTAGGACTCCTGCTAAGCTCTCCTTT	858
	AGGGTTAC**C**GAAGAGGG	859
	CCCTCTTC**G**GTAACCCT	860
Breast Cancer Glu-1214-Stop GAG to TAG	ACCCATACACATTTGGCTCAGGGTTACCGAAGAGGGGCCAAGAAATTAGAGTCCTCAGAA**G**AGAACTTATCTAGTGAGGATGAAGAGCTTCCCTGCTTCCAACACTTGTTATTTGGTAAAG	861
	CTTTACCAAATAACAAGTGTTGGAAGCAGGGAAGCTCTTCATCCTCACTAGATAAGTTCT**C**TTCTGAGGACTCTAATTTCTTGGCCCCTCTTCGGTAACCCTGAGCCAAATGTGTATGGGT	862
	CCTCAGAA**G**AGAACTTA	863
	TAAGTTCT**C**TTCTGAGG	864
Breast Cancer Glu-1219-Asp GAG to GAC	TCAGGGTTACCGAAGAGGGGCCAAGAAATTAGAGTCCTCAGAAGAGAACTTATCTAGTGA**G**GATGAAGAGCTTCCCTGCTTCCAACACTTGTTATTTGGTAAAGTAAACAATATACCTTCT	865

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGAAGGTATATTGTTTACTTTACCAAATAACAAGTGTTGGAAG CAGGGAAGCTCTTCATC**C**TCACTAGATAAGTTCTCTTCTGAG GACTCTAATTTCTTGGCCCCTCTTCGGTAACCCTGA	866
	TCTAGTGA**G**GATGAAGA	867
	TCTTCATC**C**TCACTAGA	868
Breast Cancer Glu-1221-Stop GAA to TAA	GGTTACCGAAGAGGGGCCAAGAAATTAGAGTCCTCAGAAGA GAACTTATCTAGTGAGGAT**G**AAGAGCTTCCCTGCTTCCAACA CTTGTTATTTGGTAAAGTAAACAATATACCTTCTCAGT	869
	ACTGAGAAGGTATATTGTTTACTTTACCAAATAACAAGTGTTG GAAGCAGGGAAGCTCTT**C**ATCCTCACTAGATAAGTTCTCTTC TGAGGACTCTAATTTCTTGGCCCCTCTTCGGTAACC	870
	GTGAGGAT**G**AAGAGCTT	871
	AAGCTCTT**C**ATCCTCAC	872
Breast Cancer Glu-1250-Stop GAG to TAG	TTATTTGGTAAAGTAAACAATATACCTTCTCAGTCTACTAGGC ATAGCACCGTTGCTACC**G**AGTGTCTGTCTAAGAACACAGAGG AGAATTTATTATCATTGAAGAATAGCTTAAATGACT	873
	AGTCATTTAAGCTATTCTTCAATGATAATAAATTCTCCTCTGTG TTCTTAGACAGACACT**C**GGTAGCAACGGTGCTATGCCTAGTA GACTGAGAAGGTATATTGTTTACTTTACCAAATAA	874
	TTGCTACC**G**AGTGTCTG	875
	CAGACACT**C**GGTAGCAA	876
Breast Cancer Ser-1262-Stop TCA to TAA	CTAGGCATAGCACCGTTGCTACCGAGTGTCTGTCTAAGAACA CAGAGGAGAATTTATTAT**C**ATTGAAGAATAGCTTAAATGACTG CAGTAACCAGGTAATATTGGCAAAGGCATCTCAGGA	877
	TCCTGAGATGCCTTTGCCAATATTACCTGGTTACTGCAGTCAT TTAAGCTATTCTTCAAT**G**ATAATAAATTCTCCTCTGTGTTCTTA GACAGACACTCGGTAGCAACGGTGCTATGCCTAG	878
	TTTATTAT**C**ATTGAAGA	879
	TCTTCAAT**G**ATAATAAA	880
Breast Cancer Gln-1281-Stop CAG to TAG	TTATCATTGAAGAATAGCTTAAATGACTGCAGTAACCAGGTAA TATTGGCAAAGGCATCT**C**AGGAACATCACCTTAGTGAGGAAA CAAAATGTTCTGCTAGCTTGTTTTCTTCACAGTGCA	881
	TGCACTGTGAAGAAAACAAGCTAGCAGAACATTTTGTTTCCTC ACTAAGGTGATGTTCCT**G**AGATGCCTTTGCCAATATTACCTG GTTACTGCAGTCATTTAAGCTATTCTTCAATGATAA	882

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGGCATCT**C**AGGAACAT	883
	ATGTTCCT**G**AGATGCCT	884
Breast Cancer Gln-1313-Stop CAG to TAG	GCTAGCTTGTTTTCTTCACAGTGCAGTGAATTGGAAGACTTG ACTGCAAATACAAACACC**C**AGGATCCTTTCTTGATTGGTTCTT CCAAACAAATGAGGCATCAGTCTGAAAGCCAGGGAG	885
	CTCCCTGGCTTTCAGACTGATGCCTCATTTGTTTGGAAGAAC CAATCAAGAAAGGATCCT**G**GGTGTTTGTATTTGCAGTCAAGT CTTCCAATTCACTGCACTGTGAAGAAAACAAGCTAGC	886
	CAAACACC**C**AGGATCCT	887
	AGGATCCT**G**GGTGTTTG	888
Breast Cancer Ile-1318-Val ATT to GTT	TCACAGTGCAGTGAATTGGAAGACTTGACTGCAAATACAAAC ACCCAGGATCCTTTCTTG**A**TTGGTTCTTCCAAACAAATGAGG CATCAGTCTGAAAGCCAGGGAGTTGGTCTGAGTGACA	889
	TGTCACTCAGACCAACTCCCTGGCTTTCAGACTGATGCCTCA TTTGTTTGGAAGAACCAA**T**CAAGAAAGGATCCTGGGTGTTTG TATTTGCAGTCAAGTCTTCCAATTCACTGCACTGTGA	890
	CTTTCTTG**A**TTGGTTCT	891
	AGAACCAA**T**CAAGAAAG	892
Breast Cancer Gln-1323-Stop CAA to TAA	TTGGAAGACTTGACTGCAAATACAAACACCCAGGATCCTTTC TTGATTGGTTCTTCCAAA**C**AAATGAGGCATCAGTCTGAAAGC CAGGGAGTTGGTCTGAGTGACAAGGAATTGGTTTCAG	893
	CTGAAACCAATTCCTTGTCACTCAGACCAACTCCCTGGCTTT CAGACTGATGCCTCATTT**G**TTTGGAAGAACCAATCAAGAAAG GATCCTGGGTGTTTGTATTTGCAGTCAAGTCTTCCAA	894
	CTTCCAAA**C**AAATGAGG	895
	CCTCATTT**G**TTTGGAAG	896
Breast Cancer Arg-1347-Gly AGA to GGA	CAGTCTGAAAGCCAGGGAGTTGGTCTGAGTGACAAGGAATT GGTTTCAGATGATGAAGAA**A**GAGGAACGGGCTTGGAAGAAA ATAATCAAGAAGAGCAAAGCATGGATTCAAACTTAGGTA	897
	TACCTAAGTTTGAATCCATGCTTTGCTCTTCTTGATTATTTTCT TCCAAGCCCGTTCCTC**T**TTCTTCATCATCTGAAACCAATTCCT TGTCACTCAGACCAACTCCCTGGCTTTCAGACTG	898
	ATGAAGAA**A**GAGGAACG	899
	CGTTCCTC**T**TTCTTCAT	900

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Gln-1395-Stop CAG to TAG	GAAACAAGCGTCTCTGAAGACTGCTCAGGGCTATCCTCTCAG AGTGACATTTTAACCACT**C**AGGTAAAAAGCGTGTGTGTGTGT GCACATGCGTGTGTGTGGTGTCCTTTGCATTCAGTAG	901
	CTACTGAATGCAAAGGACACCACACACACGCATGTGCACACA CACACACGCTTTTTACCT**G**AGTGGTTAAAATGTCACTCTGAG AGGATAGCCCTGAGCAGTCTTCAGAGACGCTTGTTTC	902
	TAACCACT**C**AGGTAAAA	903
	TTTTACCT**G**AGTGGTTA	904
Breast Cancer Gln-1408-Stop CAG to TAG	TGGTGCCATTTATCGTTTTTGAAGCAGAGGGATACCATGCAA CATAACCTGATAAAGCTC**C**AGCAGGAAATGGCTGAACTAGAA GCTGTGTTAGAACAGCATGGGAGCCAGCCTTCTAACA	905
	TGTTAGAAGGCTGGCTCCCATGCTGTTCTAACACAGCTTCTA GTTCAGCCATTTCCTGCT**G**GAGCTTTATCAGGTTATGTTGCAT GGTATCCCTCTGCTTCAAAAACGATAAATGGCACCA	906
	TAAAGCTC**C**AGCAGGAA	907
	TTCCTGCT**G**GAGCTTTA	908
Breast Cancer Arg-1443-Gly CGA to GGA Arg-1443-Stop CGA to TGA	AGCCAGCCTTCTAACAGCTACCCTTCCATCATAAGTGACTCT TCTGCCCTTGAGGACCTG**C**GAAATCCAGAACAAAGCACATCA GAAAAAGGTGTGTATTGTTGGCCAAACACTGATATCT	909
	AGATATCAGTGTTTGGCCAACAATACACACCTTTTTCTGATGT GCTTTGTTCTGGATTTC**G**CAGGTCCTCAAGGGCAGAAGAGTC ACTTATGATGGAAGGGTAGCTGTTAGAAGGCTGGCT	910
	AGGACCTG**C**GAAATCCA	911
	TGGATTTC**G**CAGGTCCT	912
Breast Cancer Ser-1512-Ile AGT to ATT	CAGAATAGAAACTACCCATCTCAAGAGGAGCTCATTAAGGTT GTTGATGTGGAGGAGCAA**C**AGCTGGAAGAGTCTGGGCCACA CGATTTGACGGAAACATCTTACTTGCCAAGGCAAGATC	913
	GATCTTGCCTTGGCAAGTAAGATGTTTCCGTCAAATCGTGTG GCCCAGACTCTTCCAGCT**G**TTGCTCCTCCACATCAACAACCT TAATGAGCTCCTCTTGAGATGGGTAGTTTCTATTCTG	914
	AGGAGCAA**C**AGCTGGAA	915
	TTCCAGCT**G**TTGCTCCT	916
Breast Cancer Gln-1538-Stop CAG to TAG	ATCTTTCTAGGTCATCCCCTTCTAAATGCCCATCATTAGATGA TAGGTGGTACATGCACA**G**TTGCTCTGGGAGTCTTCAGAATAG AAACTACCCATCTCAAGAGGAGCTCATTAAGGTTGT	917

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ACAACCTTAATGAGCTCCTCTTGAGATGGGTAGTTTCTATTCT GAAGACTCCCAGAGCAA**C**TGTGCATGTACCACCTATCATCTA ATGATGGGCATTTAGAAGGGGATGACCTAGAAAGAT	918
	CATGCACA**G**TTGCTCTG	919
	CAGAGCAA**C**TGTGCATG	920
Breast Cancer Glu-1541-Stop GAG to TAG	CAGAATAGAAACTACCCATCTCAAGAGGAGCTCATTAAGGTT GTTGATGTGGAGGAGCAA**C**AGCTGGAAGAGTCTGGGCCACA CGATTTGACGGAAACATCTTACTTGCCAAGGCAAGATC	921
	GATCTTGCCTTGGCAAGTAAGATGTTTCCGTCAAATCGTGTG GCCCAGACTCTTCCAGCT**G**TTGCTCCTCCACATCAACAACCT TAATGAGCTCCTCTTGAGATGGGTAGTTTCTATTCTG	922
	AGGAGCAA**C**AGCTGGAA	923
	TTCCAGCT**G**TTGCTCCT	924
Breast Cancer Thr-1561-Ile ACC to ATC	AACTACCCATCTCAAGAGGAGCTCATTAAGGTTGTTGATGTG GAGGAGCAACAGCTGGAA**G**AGTCTGGGCCACACGATTTGAC GGAAACATCTTACTTGCCAAGGCAAGATCTAGGTAATA	925
	TATTACCTAGATCTTGCCTTGGCAAGTAAGATGTTTCCGTCAA ATCGTGTGGCCCAGACT**C**TTCCAGCTGTTGCTCCTCCACATC AACAACCTTAATGAGCTCCTCTTGAGATGGGTAGTT	926
	AGCTGGAA**G**AGTCTGGG	927
	CCCAGACT**C**TTCCAGCT	928
Breast Cancer Tyr-1563-Stop TAC to TAG	TTTGTAATTCAACATTCATCGTTGTGTAAATTAAACTTCTCCCA TTCCTTTCAGAGGGAA**C**CCCTTACCTGGAATCTGGAATCAGC CTCTTCTCTGATGACCCTGAATCTGATCCTTCTGA	929
	TCAGAAGGATCAGATTCAGGGTCATCAGAGAAGAGGCTGATT CCAGATTCCAGGTAAGGG**G**TTCCCTCTGAAAGGAATGGGAG AAGTTTAATTTACACAACGATGAATGTTGAATTACAAA	930
	AGAGGGAA**C**CCCTTACC	931
	GGTAAGGG**G**TTCCCTCT	932
Breast Cancer Leu-1564-Pro CTG to CCG	CAACATTCATCGTTGTGTAAATTAAACTTCTCCCATTCCTTTC AGAGGGAACCCCTTACC**T**GGAATCTGGAATCAGCCTCTTCTC TGATGACCCTGAATCTGATCCTTCTGAAGACAGAGC	933
	GCTCTGTCTTCAGAAGGATCAGATTCAGGGTCATCAGAGAAG AGGCTGATTCCAGATTCC**A**GGTAAGGGGTTCCCTCTGAAAG GAATGGGAGAAGTTTAATTTACACAACGATGAATGTTG	934

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CCCTTACC**T**GGAATCTG	935
	CAGATTCC**A**GGTAAGGG	936
Breast Cancer Gln-1604-Stop CAA to TAA	GCCCCAGAGTCAGCTCGTGTTGGCAACATACCATCTTCAACC TCTGCATTGAAAGTTCCC**C**AATTGAAAGTTGCAGAATCTGCC CAGAGTCCAGCTGCTGCTCATACTACTGATACTGCTG	937
	CAGCAGTATCAGTAGTATGAGCAGCAGCTGGACTCTGGGCA GATTCTGCAACTTTCAATT**G**GGGAACTTTCAATGCAGAGGTT GAAGATGGTATGTTGCCAACACGAGCTGACTCTGGGGC	938
	AAGTTCCC**C**AATTGAAA	939
	TTTCAATT**G**GGGAACTT	940
Breast Cancer Lys-1606-Glu AAA to GAA	GAGTCAGCTCGTGTTGGCAACATACCATCTTCAACCTCTGCA TTGAAAGTTCCCCAATTG**A**AAGTTGCAGAATCTGCCCAGAGT CCAGCTGCTGCTCATACTACTGATACTGCTGGGTATA	941
	TATACCCAGCAGTATCAGTAGTATGAGCAGCAGCTGGACTCT GGGCAGATTCTGCAACTT**T**CAATTGGGGAACTTTCAATGCAG AGGTTGAAGATGGTATGTTGCCAACACGAGCTGACTC	942
	CCCAATTG**A**AAGTTGCA	943
	TGCAACTT**T**CAATTGGG	944
Breast Cancer Met-1628-Thr ATG to ACG	CAGAATCTGCCCAGAGTCCAGCTGCTGCTCATACTACTGATA CTGCTGGGTATAATGCAA**T**GGAAGAAAGTGTGAGCAGGGAG AAGCCAGAATTGACAGCTTCAACAGAAAGGGTCAACAA	945
	TTGTTGACCCTTTCTGTTGAAGCTGTCAATTCTGGCTTCTCCC TGCTCACACTTTCTTCC**A**TTGCATTATACCCAGCAGTATCAGT AGTATGAGCAGCAGCTGGACTCTGGGCAGATTCTG	946
	TAATGCAA**T**GGAAGAAA	947
	TTTCTTCC**A**TTGCATTA	948
Breast Cancer Met-1628-Val ATG to GTG	GCAGAATCTGCCCAGAGTCCAGCTGCTGCTCATACTACTGAT ACTGCTGGGTATAATGCA**A**TGGAAGAAAGTGTGAGCAGGGA GAAGCCAGAATTGACAGCTTCAACAGAAAGGGTCAACA	949
	TGTTGACCCTTTCTGTTGAAGCTGTCAATTCTGGCTTCTCCCT GCTCACACTTTCTTCCA**T**TGCATTATACCCAGCAGTATCAGTA GTATGAGCAGCAGCTGGACTCTGGGCAGATTCTGC	950
	ATAATGCA**A**TGGAAGAA	951

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TTCTTCCA**T**TGCATTAT	952
Breast Cancer Pro-1637-Leu CCA to CTA	CTCATACTACTGATACTGCTGGGTATAATGCAATGGAAGAAA GTGTGAGCAGGGAGAAGC**C**AGAATTGACAGCTTCAACAGAA AGGGTCAACAAAAGAATGTCCATGGTGGTGTCTGGCCT	953
	AGGCCAGACACCACCATGGACATTCTTTTGTTGACCCTTTCT GTTGAAGCTGTCAATTCT**G**GCTTCTCCCTGCTCACACTTTCTT CCATTGCATTATACCCAGCAGTATCAGTAGTATGAG	954
	GGAGAAGC**C**AGAATTGA	955
	TCAATTCT**G**GCTTCTCC	956
Breast Cancer Met-1652-Ile ATG to ATA	GAGCAGGGAGAAGCCAGAATTGACAGCTTCAACAGAAAGGG TCAACAAAAGAATGTCCAT**G**GTGGTGTCTGGCCTGACCCCAG AAGAATTTGTGAGTGTATCCATATGTATCTCCCTAATG	957
	CATTAGGGAGATACATATGGATACACTCACAAATTCTTCTGG GGTCAGGCCAGACACCAC**C**ATGGACATTCTTTTGTTGACCCT TTCTGTTGAAGCTGTCAATTCTGGCTTCTCCCTGCTC	958
	ATGTCCAT**G**GTGGTGTC	959
	GACACCAC**C**ATGGACAT	960
Breast Cancer Glu-1694-Stop GAG to TAG	CACTTCCTGATTTTGTTTTCAACTTCTAATCCTTTGAGTGTTTT TCATTCTGCAGATGCT**G**AGTTTGTGTGTGAACGGACACTGAA ATATTTTCTAGGAATTGCGGGAGGAAAATGGGTAG	961
	CTACCCATTTTCCTCCCGCAATTCCTAGAAAATATTTCAGTGT CCGTTCACACACAAACT**C**AGCATCTGCAGAATGAAAAACACT CAAAGGATTAGAAGTTGAAAACAAAATCAGGAAGTG	962
	CAGATGCT**G**AGTTTGTG	963
	CACAAACT**C**AGCATCTG	964
Breast Cancer Gly-1706-Glu GGA to GAA	GTGTTTTTCATTCTGCAGATGCTGAGTTTGTGTGTGAACGGA CACTGAAATATTTTCTAG**G**AATTGCGGGAGGAAAATGGGTAG TTAGCTATTTCTGTAAGTATAATACTATTTCTCCCCT	965
	AGGGGAGAAATAGTATTATACTTACAGAAATAGCTAACTACCC ATTTTCCTCCCGCAATT**C**CTAGAAAATATTTCAGTGTCCGTTC ACACACAAACTCAGCATCTGCAGAATGAAAAACAC	966
	TTTTCTAG**G**AATTGCGG	967
	CCGCAATT**C**CTAGAAAA	968

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Ala-1708-Glu GCG to GAG	TTCATTCTGCAGATGCTGAGTTTGTGTGTGAACGGACACTGA AATATTTTCTAGGAATTG**C**GGGAGGAAAATGGGTAGTTAGCT ATTTCTGTAAGTATAATACTATTTCTCCCCTCCTCCC	969
	GGGAGGAGGGGAGAAATAGTATTATACTTACAGAAATAGCTA ACTACCCATTTTCCTCCC**G**CAATTCCTAGAAAATATTTCAGTG TCCGTTCACACACAAACTCAGCATCTGCAGAATGAA	970
	AGGAATTG**C**GGGAGGAA	971
	TTCCTCCC**G**CAATTCCT	972
Breast Cancer Val-1713-Ala GTA to GCA	CTGAGTTTGTGTGTGAACGGACACTGAAATATTTTCTAGGAAT TGCGGGAGGAAAATGGG**T**AGTTAGCTATTTCTGTAAGTATAA TACTATTTCTCCCCTCCTCCCTTTAACACCTCAGAA	973
	TTCTGAGGTGTTAAAGGGAGGAGGGGAGAAATAGTATTATAC TTACAGAAATAGCTAACT**A**CCCATTTTCCTCCCGCAATTCCTA GAAAATATTTCAGTGTCCGTTCACACACAAACTCAG	974
	AAAATGGG**T**AGTTAGCT	975
	AGCTAACT**A**CCCATTTT	976
Breast Cancer Trp-1718-Stop TGG to TAG	AACGGACACTGAAATATTTTCTAGGAATTGCGGGAGGAAAAT GGGTAGTTAGCTATTTCT**G**TAAGTATAATACTATTTCTCCCCT CCTCCCTTTAACACCTCAGAATTGCATTTTTACACC	977
	GGTGTAAAAATGCAATTCTGAGGTGTTAAAGGGAGGAGGGG AGAAATAGTATTATACTTA**C**AGAAATAGCTAACTACCCATTTTC CTCCCGCAATTCCTAGAAAATATTTCAGTGTCCGTT	978
	CTATTTCT**G**TAAGTATA	979
	TATACTTA**C**AGAAATAG	980
Breast Cancer Glu-1725-Stop GAA to TAA	TTCTGCTGTATGTAACCTGTCTTTTCTATGATCTCTTTAGGGG TGACCCAGTCTATTAAA**G**AAAGAAAAATGCTGAATGAGGTAA GTACTTGATGTTACAAACTAACCAGAGATATTCATT	981
	AATGAATATCTCTGGTTAGTTTGTAACATCAAGTACTTACCTC ATTCAGCATTTTTCTTT**C**TTTAATAGACTGGGTCACCCCTAAA GAGATCATAGAAAAGACAGGTTACATACAGCAGAA	982
	CTATTAAA**G**AAAGAAAA	983
	TTTTCTTT**C**TTTAATAG	984
Breast Cancer Lys-1727-Stop AAA to TAA	TGTATGTAACCTGTCTTTTCTATGATCTCTTTAGGGGTGACCC AGTCTATTAAAGAAAGA**A**AAATGCTGAATGAGGTAAGTACTTG ATGTTACAAACTAACCAGAGATATTCATTCAGTCA	985

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TGACTGAATGAATATCTCTGGTTAGTTTGTAACATCAAGTACT TACCTCATTCAGCATTTT**T**TCTTTCTTTAATAGACTGGGTCACC CCTAAAGAGATCATAGAAAAGACAGGTTACATACA	986
	AAGAAAGA**A**AAATGCTG	987
	CAGCATTTT**T**TCTTTCTT	988
Breast Cancer Pro-1749-Arg CCA to CGA	TCTTTCAGCATGATTTTGAAGTCAGAGGAGATGTGGTCAATG GAAGAAACCACCAAGGTC**C**AAAGCGAGCAAGAGAATCCCAG GACAGAAAGGTAAAGCTCCCTCCCTCAAGTTGACAAAA	989
	TTTTGTCAACTTGAGGGAGGGAGCTTTACCTTTCTGTCCTGG GATTCTCTTGCTCGCTTT**G**GACCTTGGTGGTTTCTTCCATTGA CCACATCTCCTCTGACTTCAAAATCATGCTGAAAGA	990
	CCAAGGTC**C**AAAGCGAG	991
	CTCGCTTT**G**GACCTTGG	992
Breast Cancer Arg-1751-Stop CGA to TGA	CAGCATGATTTTGAAGTCAGAGGAGATGTGGTCAATGGAAGA AACCACCAAGGTCCAAAG**C**GAGCAAGAGAATCCCAGGACAG AAAGGTAAAGCTCCCTCCCTCAAGTTGACAAAAATCTC	993
	GAGATTTTTGTCAACTTGAGGGAGGGAGCTTTACCTTTCTGT CCTGGGATTCTCTTGCTC**G**CTTTGGACCTTGGTGGTTTCTTC CATTGACCACATCTCCTCTGACTTCAAAATCATGCTG	994
	GTCCAAAG**C**GAGCAAGA	995
	TCTTGCTC**G**CTTTGGAC	996
Breast Cancer Gln-1756-Stop CAG to TAG	GTCAGAGGAGATGTGGTCAATGGAAGAAACCACCAAGGTCC AAAGCGAGCAAGAGAATCC**C**AGGACAGAAAGGTAAAGCTCC CTCCCTCAAGTTGACAAAAATCTCACCCCACCACTCTGT	997
	ACAGAGTGGTGGGGTGAGATTTTTGTCAACTTGAGGGAGGG AGCTTTACCTTTCTGTCCT**G**GGATTCTCTTGCTCGCTTTGGA CCTTGGTGGTTTCTTCCATTGACCACATCTCCTCTGAC	998
	GAGAATCC**C**AGGACAGA	999
	TCTGTCCT**G**GGATTCTC	1000
Breast Cancer Met-1775-Arg ATG to AGG	CTCTCTTCTTCCAGATCTTCAGGGGGCTAGAAATCTGTTGCT ATGGGCCCTTCACCAACA**T**GCCCACAGGTAAGAGCCTGGGA GAACCCCAGAGTTCCAGCACCAGCCTTTGTCTTACATA	1001
	TATGTAAGACAAAGGCTGGTGCTGGAACTCTGGGGTTCTCCC AGGCTCTTACCTGTGGGC**A**TGTTGGTGAAGGGCCCATAGCA ACAGATTTCTAGCCCCCTGAAGATCTGGAAGAAGAGAG	1002

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
-	CACCAACA**T**GCCCACAG	1003
	CTGTGGGC**A**TGTTGGTG	1004
Breast Cancer Trp-1782-Stop TGG to TGA	AGTATGCAGATTACTGCAGTGATTTTACATCTAAATGTCCATT TTAGATCAACTGGAATG**G**ATGGTACAGCTGTGTGGTGCTTCT GTGGTGAAGGAGCTTTCATCATTCACCCTTGGCACA	1005
	TGTGCCAAGGGTGAATGATGAAAGCTCCTTCACCACAGAAGC ACCACACAGCTGTACCAT**C**CATTCCAGTTGATCTAAAATGGA CATTTAGATGTAAAATCACTGCAGTAATCTGCATACT	1006
	CTGGAATG**G**ATGGTACA	1007
	TGTACCAT**C**CATTCCAG	1008
Breast Cancer Gln-1785-His CAG to CAT	ATTACTGCAGTGATTTTACATCTAAATGTCCATTTTAGATCAAC TGGAATGGATGGTACA**G**CTGTGTGGTGCTTCTGTGGTGAAG GAGCTTTCATCATTCACCCTTGGCACAGTAAGTATT	1009
	AATACTTACTGTGCCAAGGGTGAATGATGAAAGCTCCTTCAC CACAGAAGCACCACACAG**C**TGTACCATCCATTCCAGTTGATC TAAAATGGACATTTAGATGTAAAATCACTGCAGTAAT	1010
	ATGGTACA**G**CTGTGTGG	1011
	CCACACAG**C**TGTACCAT	1012
Breast Cancer Glu-1794-Asp GAG to GAT	GTCCATTTTAGATCAACTGGAATGGATGGTACAGCTGTGTGG TGCTTCTGTGGTGAAGGA**G**CTTTCATCATTCACCCTTGGCAC AGTAAGTATTGGGTGCCCTGTCAGAGAGGGAGGACAC	1013
	GTGTCCTCCCTCTCTGACAGGGCACCCAATACTTACTGTGCC AAGGGTGAATGATGAAAG**C**TCCTTCACCACAGAAGCACCACA CAGCTGTACCATCCATTCCAGTTGATCTAAAATGGAC	1014
	GTGAAGGA**G**CTTTCATC	1015
	GATGAAAG**C**TCCTTCAC	1016
Breast Cancer Arg-1835-Stop CGA to TGA	CTCTGCTTGTGTTCTCTGTCTCCAGCAATTGGGCAGATGTGT GAGGCACCTGTGGTGACC**C**GAGAGTGGGTGTTGGACAGTGT AGCACTCTACCAGTGCCAGGAGCTGGACACCTACCTGA	1017
	TCAGGTAGGTGTCCAGCTCCTGGCACTGGTAGAGTGCTACA CTGTCCAACACCCACTCTC**G**GGTCACCACAGGTGCCTCACA CATCTGCCCAATTGCTGGAGACAGAGAACACAAGCAGAG	1018
	TGGTGACC**C**GAGAGTGG	1019
	CCACTCTC**G**GGTCACCA	1020

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Trp-1837-Arg TGG to CGG	TTGTGTTCTCTGTCTCCAGCAATTGGGCAGATGTGTGAGGCA CCTGTGGTGACCCGAGAGTGGGTGTTGGACAGTGTAGCACT CTACCAGTGCCAGGAGCTGGACACCTACCTGATACCCC	1021
	GGGGTATCAGGTAGGTGTCCAGCTCCTGGCACTGGTAGAGT GCTACACTGTCCAACACCCACTCTCGGGTCACCACAGGTGC CTCACACATCTGCCCAATTGCTGGAGACAGAGAACACAA	1022
	CCCGAGAGTGGGTGTTG	1023
	CAACACCCACTCTCGGG	1024
Breast Cancer Trp-1837-Stop TGG to TAG	TGTGTTCTCTGTCTCCAGCAATTGGGCAGATGTGTGAGGCAC CTGTGGTGACCCGAGAGTGGGTGTTGGACAGTGTAGCACTC TACCAGTGCCAGGAGCTGGACACCTACCTGATACCCCA	1025
	TGGGGTATCAGGTAGGTGTCCAGCTCCTGGCACTGGTAGAG TGCTACACTGTCCAACACCCACTCTCGGGTCACCACAGGTG CCTCACACATCTGCCCAATTGCTGGAGACAGAGAACACA	1026
	CCGAGAGTGGGTGTTGG	1027
	CCAACACCCACTCTCGG	1028

Table 15
BRCA2 Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast cancer PHE32LEU TTT to CTT	GTTAAAACTAAGGTGGGATTTTTTTTTTTAAATAGATTTAGGAC CAATAAGTCTTAATTGGTTTGAAGAACTTTCTTCAGAAGCTCC ACCCTATAATTCTGAACCTGCAGAAGAATCTGAAC	1029
	GTTCAGATTCTTCTGCAGGTTCAGAATTATAGGGTGGAGCTT CTGAAGAAAGTTCTTCAAACCAATTAAGACTTATTGGTCCTAA ATCTATTTAAAAAAAAAAATCCCACCTTAGTTTTAAC	1030
	TTAATTGGTTTGAAGAA	1031
	TTCTTCAAACCAATTAA	1032
Breast cancer TYR42CYS TAT to TGT	TAGATTTAGGACCAATAAGTCTTAATTGGTTTGAAGAACTTTC TTCAGAAGCTCCACCCTATAATTCTGAACCTGCAGAAGAATC TGAACATAAAAACAACAATTACGAACCAAACCTATT	1033

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AATAGGTTTGGTTCGTAATTGTTGTTTTTATGTTCAGATTCTTC TGCAGGTTCAGAATTA**T**AGGGTGGAGCTTCTGAAGAAAGTTC TTCAAACCAATTAAGACTTATTGGTCCTAAATCTA	1034
	TCCACCCT**A**TAATTCTG	1035
	CAGAATTA**T**AGGGTGGA	1036
Breast cancer LYS53ARG AAA to AGA	AAGAACTTTCTTCAGAAGCTCCACCCTATAATTCTGAACCTGC AGAAGAATCTGAACATA**A**AAACAACAATTACGAACCAAACCTA TTTAAAACTCCACAAAGGAAACCATCTTATAATCA	1037
	TGATTATAAGATGGTTTCCTTTGTGGAGTTTTAAATAGGTTTG GTTCGTAATTGTTGTTTT**T**ATGTTCAGATTCTTCTGCAGGTTC AGAATTATAGGGTGGAGCTTCTGAAGAAAGTTCTT	1038
	TGAACATA**A**AAACAACA	1039
	TGTTGTTTT**T**ATGTTCA	1040
Breast cancer Phe81Leu TTC to CTC	CTATTTAAAACTCCACAAAGGAAACCATCTTATAATCAGCTGG CTTCAACTCCAATAATA**T**TCAAAGAGCAAGGGCTGACTCTGC CGCTGTACCAATCTCCTGTAAAAGAATTAGATAAAT	1041
	ATTTATCTAATTCTTTTACAGGAGATTGGTACAGCGGCAGAGT CAGCCCTTGCTCTTTGA**A**TATTATTGGAGTTGAAGCCAGCTG ATTATAAGATGGTTTCCTTTGTGGAGTTTTAAATAG	1042
	CAATAATA**T**TCAAAGAG	1043
	CTCTTTGA**A**TATTATTG	1044
Breast cancer TRP194TERM TGG to TAG	GTCAGACACCAAAACATATTTCTGAAAGTCTAGGAGCTGAGG TGGATCCTGATATGTCTT**G**GTCAAGTTCTTTAGCTACACCACC CACCCTTAGTTCTACTGTGCTCATAGGTAATAATAG	1045
	CTATTATTACCTATGAGCACAGTAGAACTAAGGGTGGGTGGT GTAGCTAAAGAACTTGAC**C**AAGACATATCAGGATCCACCTCA GCTCCTAGACTTTCAGAAATATGTTTTGGTGTCTGAC	1046
	TATGTCTT**G**GTCAAGTT	1047
	AACTTGAC**C**AAGACATA	1048
Breast cancer PRO201ARG CCA to CGA	CTGAAAGTCTAGGAGCTGAGGTGGATCCTGATATGTCTTGGT CAAGTTCTTTAGCTACAC**C**ACCCACCCTTAGTTCTACTGTGCT CATAGGTAATAATAGCAAATGTGTATTTACAAGAAA	1049
	TTTCTTGTAAATACACATTTGCTATTATTACCTATGAGCACAGT AGAACTAAGGGTGGGT**G**GTGTAGCTAAAGAACTTGACCAAGA CATATCAGGATCCACCTCAGCTCCTAGACTTTCAG	1050

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGCTACAC**C**ACCCACCC	1051
	GGGTGGGT**G**GTGTAGCT	1052
Breast cancer Pro222Ser CCT to TCT	ACAATACACATAAATTTTTATCTTACAGTCAGAAATGAAGAAG CATCTGAAACTGTATTT**C**CTCATGATACTACTGCTGTAAGTAA ATATGACATTGATTAGACTGTTGAAATTGCTAACA	1053
	TGTTAGCAATTTCAACAGTCTAATCAATGTCATATTTACTTACA GCAGTAGTATCATGAG**G**AAATACAGTTTCAGATGCTTCTTCAT TTCTGACTGTAAGATAAAAATTTATGTGTATTGT	1054
	CTGTATTT**C**CTCATGAT	1055
	ATCATGAG**G**AAATACAG	1056
Breast cancer Leu-414-Term TTG to TAG	AATGGTCTCAACTAACCCTTTCAGGTCTAAATGGAGCCCAGA TGGAGAAAATACCCCTAT**T**GCATATTTCTTCATGTGACCAAAA TATTTCAGAAAAAGACCTATTAGACACAGAGAACAA	1057
	TTGTTCTCTGTGTCTAATAGGTCTTTTTCTGAAATATTTTGGTC ACATGAAGAAATATGC**A**ATAGGGGTATTTTCTCCATCTGGGC TCCATTTAGACCTGAAAGGGTTAGTTGAGACCATT	1058
	ACCCCTAT**T**GCATATTT	1059
	AAATATGC**A**ATAGGGGT	1060
Breast cancer, male Cys554Trp TGT to TGG	AGCCTCTGAAAGTGGACTGGAAATACATACTGTTTGCTCACA GAAGGAGGACTCCTTATG**T**CCAAATTTAATTGATAATGGAAG CTGGCCAGCCACCACCACACAGAATTCTGTAGCTTTG	1061
	CAAAGCTACAGAATTCTGTGTGGTGGTGGCTGGCCAGCTTC CATTATCAATTAAATTTGG**A**CATAAGGAGTCCTCCTTCTGTGA GCAAACAGTATGTATTTCCAGTCCACTTTCAGAGGCT	1062
	TCCTTATG**T**CCAAATTT	1063
	AAATTTGG**A**CATAAGGA	1064
Breast cancer Lys944Term AAA to TAA	AACTCTACCATGGTTTTATATGGAGACACAGGTGATAAACAA GCAACCCAAGTGTCAATT**A**AAAAAGATTTGGTTTATGTTCTTG CAGAGGAGAACAAAAATAGTGTAAAGCAGCATATAA	1065
	TTATATGCTGCTTTACACTATTTTTGTTCTCCTCTGCAAGAAC ATAAACCAAATCTTTTT**T**AATTGACACTTGGGTTGCTTGTTTAT CACCTGTGTCTCCATATAAAACCATGGTAGAGTT	1066
	TGTCAATT**A**AAAAAGAT	1067
	ATCTTTTT**T**AATTGACA	1068

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast cancer, male Glu1320Term GAA to TAA	ATGACTACTGGCACTTTTGTTGAAGAAATTACTGAAAATTACA AGAGAAATACTGAAAAT**G**AAGATAACAAATATACTGCTGCCAG TAGAAATTCTCATAACTTAGAATTTGATGGCAGTG	1069
	CACTGCCATCAAATTCTAAGTTATGAGAATTTCTACTGGCAGC AGTATATTTGTTATCTT**C**ATTTTCAGTATTTCTCTTGTAATTTTC AGTAATTTCTTCAACAAAAGTGCCAGTAGTCAT	1070
	CTGAAAAT**G**AAGATAAC	1071
	GTTATCTT**C**ATTTTCAG	1072
Breast cancer Glu1876Term GAA to TAA	CATGAAACAATTAAAAAAGTGAAAGACATATTTACAGACAGTT TCAGTAAAGTAATTAAG**G**AAAACAACGAGAATAAATCAAAAAT TTGCCAAACGAAAATTATGGCAGGTTGTTACGAGG	1073
	CCTCGTAACAACCTGCCATAATTTTCGTTTGGCAAATTTTTGA TTTATTCTCGTTGTTTT**C**CTTAATTACTTTACTGAAACTGTCTG TAAATATGTCTTTCACTTTTTTAATTGTTTCATG	1074
	TAATTAAG**G**AAAACAAC	1075
	GTTGTTTT**C**CTTAATTA	1076
Breast cancer Ser1882Term TCA to TAA	TGAAAGACATATTTACAGACAGTTTCAGTAAAGTAATTAAGGA AAACAACGAGAATAAAT**C**AAAAATTTGCCAAACGAAAATTATG GCAGGTTGTTACGAGGCATTGGATGATTCAGAGGA	1077
	TCCTCTGAATCATCCAATGCCTCGTAACAACCTGCCATAATTT TCGTTTGGCAAATTTTT**G**ATTTATTCTCGTTGTTTTCCTTAATT ACTTTACTGAAACTGTCTGTAAATATGTCTTTCA	1078
	GAATAAAT**C**AAAAATTT	1079
	AAATTTTT**G**ATTTATTC	1080
Breast cancer Glu1953Term GAA to TAA	AACCAAAATATGTCTGGATTGGAGAAAGTTTCTAAAATATCAC CTTGTGATGTTAGTTTG**G**AAACTTCAGATATATGTAAATGTAG TATAGGGAAGCTTCATAAGTCAGTCTCATCTGCAA	1081
	TTGCAGATGAGACTGACTTATGAAGCTTCCCTATACTACATTT ACATATATCTGAAGTTT**C**CAAACTAACATCACAAGGTGATATT TTAGAAACTTTCTCCAATCCAGACATATTTTGGTT	1082
	TTAGTTTG**G**AAACTTCA	1083
	TGAAGTTT**C**CAAACTAA	1084
Breast cancer Ser1970Term TCA to TAA	TTAGTTTGGAAACTTCAGATATATGTAAATGTAGTATAGGGAA GCTTCATAAGTCAGTCT**C**ATCTGCAAATACTTGTGGGATTTTT AGCACAGCAAGTGGAAAATCTGTCCAGGTATCAGA	1085

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TCTGATACCTGGACAGATTTTCCACTTGCTGTGCTAAAAATCC CACAAGTATTTGCAGAT**G**AGACTGACTTATGAAGCTTCCCTAT ACTACATTTACATATATCTGAAGTTTCCAAACTAA	1086
	GTCAGTCT**C**ATCTGCAA	1087
	TTGCAGAT**G**AGACTGAC	1088
Breast cancer Gln1987Term CAG to TAG	AAGTCAGTCTCATCTGCAAATACTTGTGGGATTTTTAGCACAG CAAGTGGAAAATCTGTC**C**AGGTATCAGATGCTTCATTACAAAA CGCAAGACAAGTGTTTTCTGAAATAGAAGATAGTA	1089
	TACTATCTTCTATTTCAGAAAACACTTGTCTTGCGTTTTGTAAT GAAGCATCTGATACCT**G**GACAGATTTTCCACTTGCTGTGCTA AAAATCCCACAAGTATTTGCAGATGAGACTGACTT	1090
	AATCTGTC**C**AGGTATCA	1091
	TGATACCT**G**GACAGATT	1092
Breast cancer Ala2466Val GCA to GTA	AAAATAAGATTAATGACAATGAGATTCATCAGTTTAACAAAAA CAACTCCAATCAAGCAG**C**AGCTGTAACTTTCACAAAGTGTGA AGAAGAACCTTTAGGTATTGTATGACAATTTGTGTG	1093
	CACACAAATTGTCATACAATACCTAAAGGTTCTTCTTCACACT TTGTGAAAGTTACAGCT**G**CTGCTTGATTGGAGTTGTTTTTGTT AAACTGATGAATCTCATTGTCATTAATCTTATTTT	1094
	TCAAGCAG**C**AGCTGTAA	1095
	TTACAGCT**G**CTGCTTGA	1096
Breast cancer Arg2520Term CGA to TGA	AGGCAACGCGTCTTTCCACAGCCAGGCAGTCTGTATCTTGCA AAAACATCCACTCTGCCT**C**GAATCTCTCTGAAAGCAGCAGTA GGAGGCCAAGTCCCCTCTGCGTGTCCTCATAAACAGG	1097
	CCTGTTTATGAGGACACGCAGAGGGGACTTGGCCTCCTACT GCTGCTTTCAGAGAGATTC**G**AGGCAGAGTGGATGTTTTTGCA AGATACAGACTGCCTGGCTGTGGAAAGACGCGTTGCCT	1098
	CTCTGCCT**C**GAATCTCT	1099
	AGAGATTC**G**AGGCAGAG	1100
Breast cancer Gln2714Term CAA to TAA	ATTTCATTGAGCGCAAATATATCTGAAACTTCTAGCAATAAAA CTAGTAGTGCAGATACC**C**AAAAAGTGGCCATTATTGAACTTA CAGATGGGTGGTATGCTGTTAAGGCCCAGTTAGATC	1101
	GATCTAACTGGGCCTTAACAGCATACCACCCATCTGTAAGTT CAATAATGGCCACTTTTT**G**GGTATCTGCACTACTAGTTTTATT GCTAGAAGTTTCAGATATATTTGCGCTCAATGAAAT	1102

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CAGATACC**C**AAAAAGTG	1103
	CACTTTTT**G**GGTATCTG	1104
Breast cancer Leu2776Term TTA to TGA	CAGAACTGGTGGGCTCTCCTGATGCCTGTACACCTCTTGAAG CCCCAGAATCTCTTATGT**T**AAAGGTAAATTAATTTGCACTCTT GGTAAAAATCAGTCATTGATTCAGTTAAATTCTAGA	1105
	TCTAGAATTTAACTGAATCAATGACTGATTTTTACCAAGAGTG CAAATTAATTTACCTTT**A**ACATAAGAGATTCTGGGGCTTCAAG AGGTGTACAGGCATCAGGAGAGCCCACCAGTTCTG	1106
	TCTTATGT**T**AAAGATTT	1107
	AAATCTTT**A**ACATAAGA	1108
Breast cancer Gln2893Term CAG to TAG	CCTTTTGTTTTCTTAGAAAACACAACAAAACCATATTTACCATC ACGTGCACTAACAAGA**C**AGCAAGTTCGTGCTTTGCAAGATGG TGCAGAGCTTTATGAAGCAGTGAAGAATGCAGCAG	1109
	CTGCTGCATTCTTCACTGCTTCATAAAGCTCTGCACCATCTTG CAAAGCACGAACTTGCT**G**TCTTGTTAGTGCACGTGATGGTAA ATATGGTTTTGTTGTGTTTTCTAAGAAAACAAAAGG	1110
	TAACAAGA**C**AGCAAGTT	1111
	AACTTGCT**G**TCTTGTTA	1112
Breast cancer Ala2951Thr GCC to ACC	AATCACAGGCAAATGTTGAATGATAAGAAACAAGCTCAGATC CAGTTGGAAATTAGGAAG**G**CCATGGAATCTGCTGAACAAAAG GAACAAGGTTTATCAAGGGATGTCACAACCGTGTGGA	1113
	TCCACACGGTTGTGACATCCCTTGATAAACCTTGTTCCTTTTG TTCAGCAGATTCCATGG**C**CTTCCTAATTTCCAACTGGATCTGA GCTTGTTTCTTATCATTCAACATTTGCCTGTGATT	1114
	TTAGGAAG**G**CCATGGAA	1115
	TTCCATGG**C**CTTCCTAA	1116
Breast cancer Met3118Thr ATG to ACG	ACAATTTACTGGCAATAAAGTTTTGGATAGACCTTAATGAGGA CATTATTAAGCCTCATA**T**GTTAATTGCTGCAAGCAACCTCCAG TGGCGACCAGAATCCAAATCAGGCCTTCTTACTTT	1117
	AAAGTAAGAAGGCCTGATTTGGATTCTGGTCGCCACTGGAG GTTGCTTGCAGCAATTAAC**A**TATGAGGCTTAATAATGTCCTCA TTAAGGTCTATCCAAAACTTTATTGCCAGTAAATTGT	1118
	GCCTCATA**T**GTTAATTG	1119
	CAATTAAC**A**TATGAGGC	1120

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast cancer Thr3401Met ACG to ATG	GACTGAAACGACGTTGTACTACATCTCTGATCAAAGAACAGG AGAGTTCCCAGGCCAGTA**C**GGAAGAATGTGAGAAAAATAAGC AGGACACAATTACAACTAAAAAATATATCTAAGCATT	1121
	AATGCTTAGATATATTTTTTAGTTGTAATTGTGTCCTGCTTATT TTTCTCACATTCTTCC**G**TACTGGCCTGGGAACTCTCCTGTTCT TTGATCAGAGATGTAGTACAACGTCGTTTCAGTC	1122
	GGCCAGTA**C**GGAAGAAT	1123
	ATTCTTCC**G**TACTGGCC	1124
Breast cancer Ile3412Val ATT to GTT	AAAGAACAGGAGAGTTCCCAGGCCAGTACGGAAGAATGTGA GAAAAATAAGCAGGACACA**A**TTACAACTAAAAAATATATCTAA GCATTTGCAAAGGCGACAATAAATTATTGACGCTTAA	1125
	TTAAGCGTCAATAATTTATTGTCGCCTTTGCAAATGCTTAGAT ATATTTTTTAGTTGTAA**T**TGTGTCCTGCTTATTTTTCTCACATT CTTCCGTACTGGCCTGGGAACTCTCCTGTTCTTT	1126
	AGGACACA**A**TTACAACT	1127
	AGTTGTAA**T**TGTGTCCT	1128

EXAMPLE 9
Cystic Fibrosis - CFTR

Cystic fibrosis is a lethal disease affecting approximately one in 2,500 live Caucasian births and is the most common autosomal recessive disease in Caucasians. Patients with this disease have reduced chloride ion permeability in the secretory and absorptive cells of organs with epithelial cell linings, including the airways, pancreas, intestine, sweat glands and male genital tract. This, in turn, reduces the transport of water across the epithelia. The lungs and the GI tract are the predominant organ systems affected in this disease and the pathology is characterized by blocking of the respiratory and GI tracts with viscous mucus. The chloride impermeability in affected tissues is due to mutations in a specific chloride channel, the cystic fibrosis transmembrane conductance regulator protein (CFTR), which prevents normal passage of chloride ions through the cell membrane (Welsh et al., Neuron, 8:821-829 (1992)). Damage to the lungs due to mucus blockage, frequent bacterial infections and inflammation is the primary cause of morbidity and mortality in CF patients and, although maintenance therapy has improved the quality of patients' lives, the median age at death is still only around 30 years. There is no effective treatment for the disease, and therapeutic research is focused on gene therapy using

exogenous transgenes in viral vectors and/or activating the defective or other chloride channels in the cell membrane to normalize chloride permeability (Tizzano et al., J. Pediat., 120:337-349 (1992)). However, the death of a teenage patient treated with an adenovirus vector carrying an exogenous CFTR gene in clinical trials in the late 1990's has impacted this area of research.

The oligonucleotides of the invention for correction of the CFTR gene are attached as a table.

Table 16
CFTR Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Ala46Asp GCT to GAT	AAGGATACAGACAGCGCCTGGAATTGTCAGACATATACCAAA TCCCTTCTGTTGATTCTG**C**TGACAATCTATCTGAAAAATTGGA AAGGTATGTTCATGTACATTGTTTAGTTGAAGAGAG	1129
	CTCTCTTCAACTAAACAATGTACATGAACATACCTTTCCAATTT TTCAGATAGATTGTCA**G**CAGAATCAACAGAAGGGATTTGGTA TATGTCTGACAATTCCAGGCGCTGTCTGTATCCTT	1130
	TGATTCTG**C**TGACAATC	1131
	GATTGTCA**G**CAGAATCA	1132
Cystic fibrosis Ser50Tyr TCT to TAT	AGCGCCTGGAATTGTCAGACATATACCAAATCCCTTCTGTTG ATTCTGCTGACAATCTAT**C**TGAAAAATTGGAAAGGTATGTTCA TGTACATTGTTTAGTTGAAGAGAGAAATTCATATTA	1133
	TAATATGAATTTCTCTCTTCAACTAAACAATGTACATGAACATA CCTTTCCAATTTTTCA**G**ATAGATTGTCAGCAGAATCAACAGAA GGGATTTGGTATATGTCTGACAATTCCAGGCGCT	1134
	CAATCTAT**C**TGAAAAAT	1135
	ATTTTTCA**G**ATAGATTG	1136
Congenital absence of vas deferens Glu56Lys GAA-AAA	AGGACAACTAAAATATTTGCACATGCAACTTATTGGTCCCACT TTTTATTCTTTTGCAGA**G**AATGGGATAGAGAGCTGGCTTCAAA GAAAAATCCTAAACTCATTAATGCCCTTCGGCGAT	1137
	ATCGCCGAAGGGCATTAATGAGTTTAGGATTTTTCTTTGAAGC CAGCTCTCTATCCCATT**C**TCTGCAAAAGAATAAAAAGTGGGA CCAATAAGTTGCATGTGCAAATATTTTAGTTGTCCT	1138
	TTTGCAGA**G**AATGGGAT	1139
	ATCCCATT**C**TCTGCAAA	1140

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Trp57Gly TGG to GGG	AGGACAACTAAAATATTTGCACATGCAACTTATTGGTCCCACTTTTTATTCTTTTGCAGA**G**AATGGGATAGAGAGCTGGCTTCAAAGAAAAATCCTAAACTCATTAATGCCCTTCGGCGAT	1141
	ATCGCCGAAGGGCATTAATGAGTTTAGGATTTTTCTTTGAAGCCAGCTCTCTATCCCATT**C**TCTGCAAAAGAATAAAAAGTGGGACCAATAAGTTGCATGTGCAAATATTTTAGTTGTCCT	1142
	TTTGCAGA**G**AATGGGAT	1143
	ATCCCATT**C**TCTGCAAA	1144
Cystic fibrosis Trp57Term TGG to TGA	AACTAAAATATTTGCACATGCAACTTATTGGTCCCACTTTTTATTCTTTTGCAGAGAATG**G**GATAGAGAGCTGGCTTCAAAGAAAAATCCTAAACTCATTAATGCCCTTCGGCGATGTTTT	1145
	AAAACATCGCCGAAGGGCATTAATGAGTTTAGGATTTTTCTTTGAAGCCAGCTCTCTATC**C**CATTCTCTGCAAAAGAATAAAAAGTGGGACCAATAAGTTGCATGTGCAAATATTTTAGTT	1146
	AGAGAATG**G**GATAGAGA	1147
	TCTCTATC**C**CATTCTCT	1148
Congenital absence of vas deferens Asp58Asn GAT to AAT	ACTAAAATATTTGCACATGCAACTTATTGGTCCCACTTTTTATTCTTTTGCAGAGAATGG**G**ATAGAGAGCTGGCTTCAAAGAAAAATCCTAAACTCATTAATGCCCTTCGGCGATGTTTTT	1149
	AAAAACATCGCCGAAGGGCATTAATGAGTTTAGGATTTTTCTTTGAAGCCAGCTCTCTAT**C**CCATTCTCTGCAAAAGAATAAAAAGTGGGACCAATAAGTTGCATGTGCAAATATTTTAGT	1150
	GAGAATGG**G**ATAGAGAG	1151
	CTCTCTAT**C**CCATTCTC	1152
Cystic fibrosis Glu60Term GAG to TAG	ATATTTGCACATGCAACTTATTGGTCCCACTTTTTATTCTTTTGCAGAGAATGGGATAGA**G**AGCTGGCTTCAAAGAAAAATCCTAAACTCATTAATGCCCTTCGGCGATGTTTTTTCTGGA	1153
	TCCAGAAAAAACATCGCCGAAGGGCATTAATGAGTTTAGGATTTTTCTTTGAAGCCAGCT**C**TCTATCCCATTCTCTGCAAAAGAATAAAAAGTGGGACCAATAAGTTGCATGTGCAAATAT	1154
	GGGATAGA**G**AGCTGGCT	1155
	AGCCAGCT**C**TCTATCCC	1156

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Pro67Leu CCT to CTT	GGTCCCACTTTTTATTCTTTTGCAGAGAATGGGATAGAGAGC TGGCTTCAAAGAAAAATC**C**TAAACTCATTAATGCCCTTCGGC GATGTTTTTTCTGGAGATTTATGTTCTATGGAATCTT	1157
	AAGATTCCATAGAACATAAATCTCCAGAAAAAACATCGCCGAA GGGCATTAATGAGTTTA**G**GATTTTTCTTTGAAGCCAGCTCTCT ATCCCATTCTCTGCAAAAGAATAAAAAGTGGGACC	1158
	GAAAAATC**C**TAAACTCA	1159
	TGAGTTTA**G**GATTTTTC	1160
Cystic fibrosis Arg74Trp CGG to TGG	TGCAGAGAATGGGATAGAGAGCTGGCTTCAAAGAAAAATCCT AAACTCATTAATGCCCTT**C**GGCGATGTTTTTTCTGGAGATTTA TGTTCTATGGAATCTTTTTATATTTAGGGGTAAGGA	1161
	TCCTTACCCCTAAATATAAAAAGATTCCATAGAACATAAATCT CCAGAAAAAACATCGCC**G**AAGGGCATTAATGAGTTTAGGATT TTTCTTTGAAGCCAGCTCTCTATCCCATTCTCTGCA	1162
	ATGCCCTT**C**GGCGATGT	1163
	ACATCGCC**G**AAGGGCAT	1164
Congenital absence of vas deferens ARG75GLN CGA to CAA	GAGAATGGGATAGAGAGCTGGCTTCAAAGAAAAATCCTAAAC TCATTAATGCCCTTCGGC**G**ATGTTTTTTCTGGAGATTTATGTT CTATGGAATCTTTTTATATTTAGGGGTAAGGATCTC	1165
	GAGATCCTTACCCCTAAATATAAAAAGATTCCATAGAACATAA ATCTCCAGAAAAAACAT**C**GCCGAAGGGCATTAATGAGTTTAG GATTTTTCTTTGAAGCCAGCTCTCTATCCCATTCTC	1166
	CCTTCGGC**G**ATGTTTTT	1167
	AAAAACAT**C**GCCGAAGG	1168
Cystic fibrosis Arg75Leu CGA to CTA	GAGAATGGGATAGAGAGCTGGCTTCAAAGAAAAATCCTAAAC TCATTAATGCCCTTCGGC**G**ATGTTTTTTCTGGAGATTTATGTT CTATGGAATCTTTTTATATTTAGGGGTAAGGATCTC	1169
	GAGATCCTTACCCCTAAATATAAAAAGATTCCATAGAACATAA ATCTCCAGAAAAAACAT**C**GCCGAAGGGCATTAATGAGTTTAG GATTTTTCTTTGAAGCCAGCTCTCTATCCCATTCTC	1170
	CCTTCGGC**G**ATGTTTTT	1171
	AAAAACAT**C**GCCGAAGG	1172
Cystic fibrosis Arg75Term CGA to TGA	AGAGAATGGGATAGAGAGCTGGCTTCAAAGAAAAATCCTAAA CTCATTAATGCCCTTCGG**C**GATGTTTTTTCTGGAGATTTATGT TCTATGGAATCTTTTTATATTTAGGGGTAAGGATCT	1173

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGATCCTTACCCCTAAATATAAAAAGATTCCATAGAACATAAATCTCCAGAAAAAACATC**G**CCGAAGGGCATTAATGAGTTTAGGATTTTTCTTTGAAGCCAGCTCTCTATCCCATTCTCT	1174
	CCCTTCGG**C**GATGTTTT	1175
	AAAACATC**G**CCGAAGGG	1176
Cystic fibrosis Gly85Glu GGA to GAA	AAAATCCTAAACTCATTAATGCCCTTCGGCGATGTTTTTTCTGGAGATTTATGTTCTATG**G**AATCTTTTTATATTTAGGGGTAAGGATCTCATTTGTACATTCATTATGTATCACATAACT	1177
	AGTTATGTGATACATAATGAATGTACAAATGAGATCCTTACCCCTAAATATAAAAAGATT**C**CATAGAACATAAATCTCCAGAAAAAACATCGCCGAAGGGCATTAATGAGTTTAGGATTTT	1178
	GTTCTATG**G**AATCTTTT	1179
	AAAAGATT**C**CATAGAAC	1180
Cystic fibrosis Gly85Val GGA to GTA	AAAATCCTAAACTCATTAATGCCCTTCGGCGATGTTTTTTCTGGAGATTTATGTTCTATG**G**AATCTTTTTATATTTAGGGGTAAGGATCTCATTTGTACATTCATTATGTATCACATAACT	1181
	AGTTATGTGATACATAATGAATGTACAAATGAGATCCTTACCCCTAAATATAAAAAGATT**C**CATAGAACATAAATCTCCAGAAAAAACATCGCCGAAGGGCATTAATGAGTTTAGGATTTT	1182
	GTTCTATG**G**AATCTTTT	1183
	AAAAGATT**C**CATAGAAC	1184
Cystic fibrosis Leu88Ser TTA to TCA	AACTCATTAATGCCCTTCGGCGATGTTTTTTCTGGAGATTTATGTTCTATGGAATCTTTT**T**ATATTTAGGGGTAAGGATCTCATTTGTACATTCATTATGTATCACATAACTATATGCATT	1185
	AATGCATATAGTTATGTGATACATAATGAATGTACAAATGAGATCCTTACCCCTAAATAT**A**AAAAGATTCCATAGAACATAAATCTCCAGAAAAAACATCGCCGAAGGGCATTAATGAGTT	1186
	AATCTTTT**T**ATATTTAG	1187
	CTAAATAT**A**AAAAGATT	1188
Cystic fibrosis Phe87Leu TTT to CTT	CCTAAACTCATTAATGCCCTTCGGCGATGTTTTTTCTGGAGATTTATGTTCTATGGAATC**T**TTTTATATTTAGGGGTAAGGATCTCATTTGTACATTCATTATGTATCACATAACTATATG	1189
	CATATAGTTATGTGATACATAATGAATGTACAAATGAGATCCTTACCCCTAAATATAAAA**A**GATTCCATAGAACATAAATCTCCAGAAAAAACATCGCCGAAGGGCATTAATGAGTTTAGG	1190

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATGGAATC**T**TTTTATAT	1191
	ATATAAAA**A**GATTCCAT	1192
Cystic fibrosis Leu88Term TTA to TGA	AACTCATTAATGCCCTTCGGCGATGTTTTTTCTGGAGATTTAT GTTCTATGGAATCTTTT**T**ATATTTAGGGGTAAGGATCTCATTT GTACATTCATTATGTATCACATAACTATATGCATT	1193
	AATGCATATAGTTATGTGATACATAATGAATGTACAAATGAGA TCCTTACCCCTAAATAT**A**AAAAGATTCCATAGAACATAAATCT CCAGAAAAAACATCGCCGAAGGGCATTAATGAGTT	1194
	AATCTTTT**T**ATATTTAG	1195
	CTAAATAT**A**AAAAGATT	1196
Cystic fibrosis Leu88Term TTA to TAA	AACTCATTAATGCCCTTCGGCGATGTTTTTTCTGGAGATTTAT GTTCTATGGAATCTTTT**T**ATATTTAGGGGTAAGGATCTCATTT GTACATTCATTATGTATCACATAACTATATGCATT	1197
	AATGCATATAGTTATGTGATACATAATGAATGTACAAATGAGA TCCTTACCCCTAAATAT**A**AAAAGATTCCATAGAACATAAATCT CCAGAAAAAACATCGCCGAAGGGCATTAATGAGTT	1198
	AATCTTTT**T**ATATTTAG	1199
	CTAAATAT**A**AAAAGATT	1200
Cystic fibrosis Gly91Arg GGG to AGG	AATGCCCTTCGGCGATGTTTTTTCTGGAGATTTATGTTCTATG GAATCTTTTTATATTTA**G**GGGTAAGGATCTCATTTGTACATTC ATTATGTATCACATAACTATATGCATTTTTGTGAT	1201
	ATCACAAAAATGCATATAGTTATGTGATACATAATGAATGTAC AAATGAGATCCTTACCC**C**TAAATATAAAAAGATTCCATAGAAC ATAAATCTCCAGAAAAAACATCGCCGAAGGGCATT	1202
	TATATTTA**G**GGGTAAGG	1203
	CCTTACCC**C**TAAATATA	1204
Cystic fibrosis Gln98Arg CAG to CGG	AATAAATGAAATTTAATTTCTCTGTTTTTCCCCTTTTGTAGGAA GTCACCAAAGCAGTAC**A**GCCTCTCTTACTGGGAAGAATCATA GCTTCCTATGACCCGGATAACAAGGAGGAACGCTC	1205
	GAGCGTTCCTCCTTGTTATCCGGGTCATAGGAAGCTATGATT CTTCCCAGTAAGAGAGGC**T**GTACTGCTTTGGTGACTTCCTAC AAAAGGGGAAAAACAGAGAAATTAAATTTCATTTATT	1206
	AGCAGTAC**A**GCCTCTCT	1207
	AGAGAGGC**T**GTACTGCT	1208

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Gln98Term CAG-TAG	AAATAAATGAAATTTAATTTCTCTGTTTTTCCCCTTTTGTAGGA AGTCACCAAAGCAGTA**C**AGCCTCTCTTACTGGGAAGAATCAT AGCTTCCTATGACCCGGATAACAAGGAGGAACGCT	1209
	AGCGTTCCTCCTTGTTATCCGGGTCATAGGAAGCTATGATTC TTCCCAGTAAGAGAGGCT**G**TACTGCTTTGGTGACTTCCTACA AAAGGGGAAAAACAGAGAAATTAAATTTCATTTATTT	1210
	AAGCAGTA**C**AGCCTCTC	1211
	GAGAGGCT**G**TACTGCTT	1212
Cystic fibrosis Ser108Phe TCC to TTC	CCCTTTTGTAGGAAGTCACCAAAGCAGTACAGCCTCTCTTAC TGGGAAGAATCATAGCTT**C**CTATGACCCGGATAACAAGGAGG AACGCTCTATCGCGATTTATCTAGGCATAGGCTTATG	1213
	CATAAGCCTATGCCTAGATAAATCGCGATAGAGCGTTCCTCC TTGTTATCCGGGTCATAG**G**AAGCTATGATTCTTCCCAGTAAG AGAGGCTGTACTGCTTTGGTGACTTCCTACAAAAGGG	1214
	CATAGCTT**C**CTATGACC	1215
	GGTCATAG**G**AAGCTATG	1216
Cystic fibrosis Tyr109Cys TAT to TGT	TTTTGTAGGAAGTCACCAAAGCAGTACAGCCTCTCTTACTGG GAAGAATCATAGCTTCCT**A**TGACCCGGATAACAAGGAGGAAC GCTCTATCGCGATTTATCTAGGCATAGGCTTATGCCT	1217
	AGGCATAAGCCTATGCCTAGATAAATCGCGATAGAGCGTTCC TCCTTGTTATCCGGGTCA**T**AGGAAGCTATGATTCTTCCCAGT AAGAGAGGCTGTACTGCTTTGGTGACTTCCTACAAAA	1218
	AGCTTCCT**A**TGACCCGG	1219
	CCGGGTCA**T**AGGAAGCT	1220
Cystic fibrosis Asp110His GAC to CAC	TTGTAGGAAGTCACCAAAGCAGTACAGCCTCTCTTACTGGGA AGAATCATAGCTTCCTAT**G**ACCCGGATAACAAGGAGGAACGC TCTATCGCGATTTATCTAGGCATAGGCTTATGCCTTC	1221
	GAAGGCATAAGCCTATGCCTAGATAAATCGCGATAGAGCGTT CCTCCTTGTTATCCGGGT**C**ATAGGAAGCTATGATTCTTCCCA GTAAGAGAGGCTGTACTGCTTTGGTGACTTCCTACAA	1222
	CTTCCTAT**G**ACCCGGAT	1223
	ATCCGGGT**C**ATAGGAAG	1224

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Congenital absence of vas deferens Pro111Leu CCG to CTG	AGGAAGTCACCAAAGCAGTACAGCCTCTCTTACTGGGAAGAA TCATAGCTTCCTATGACC**C**GGATAACAAGGAGGAACGCTCTA TCGCGATTTATCTAGGCATAGGCTTATGCCTTCTCTT	1225
	AAGAGAAGGCATAAGCCTATGCCTAGATAAATCGCGATAGAG CGTTCCTCCTTGTTATCC**G**GGTCATAGGAAGCTATGATTCTT CCCAGTAAGAGAGGCTGTACTGCTTTGGTGACTTCCT	1226
	CTATGACC**C**GGATAACA	1227
	TGTTATCC**G**GGTCATAG	1228
Cystic fibrosis Arg117Cys CGC to TGC	GTACAGCCTCTCTTACTGGGAAGAATCATAGCTTCCTATGAC CCGGATAACAAGGAGGAA**C**GCTCTATCGCGATTTATCTAGGC ATAGGCTTATGCCTTCTCTTTATTGTGAGGACACTGC	1229
	GCAGTGTCCTCACAATAAAGAGAAGGCATAAGCCTATGCCTA GATAAATCGCGATAGAGC**G**TTCCTCCTTGTTATCCGGGTCAT AGGAAGCTATGATTCTTCCCAGTAAGAGAGGCTGTAC	1230
	AGGAGGAA**C**GCTCTATC	1231
	GATAGAGC**G**TTCCTCCT	1232
Cystic fibrosis Arg117His CGC to CAC	TACAGCCTCTCTTACTGGGAAGAATCATAGCTTCCTATGACC CGGATAACAAGGAGGAAC**G**CTCTATCGCGATTTATCTAGGCA TAGGCTTATGCCTTCTCTTTATTGTGAGGACACTGCT	1233
	AGCAGTGTCCTCACAATAAAGAGAAGGCATAAGCCTATGCCT AGATAAATCGCGATAGAG**C**GTTCCTCCTTGTTATCCGGGTCA TAGGAAGCTATGATTCTTCCCAGTAAGAGAGGCTGTA	1234
	GGAGGAAC**G**CTCTATCG	1235
	CGATAGAG**C**GTTCCTCC	1236
Cystic fibrosis Arg117Leu CGC to CTC	TACAGCCTCTCTTACTGGGAAGAATCATAGCTTCCTATGACC CGGATAACAAGGAGGAAC**G**CTCTATCGCGATTTATCTAGGCA TAGGCTTATGCCTTCTCTTTATTGTGAGGACACTGCT	1237
	AGCAGTGTCCTCACAATAAAGAGAAGGCATAAGCCTATGCCT AGATAAATCGCGATAGAG**C**GTTCCTCCTTGTTATCCGGGTCA TAGGAAGCTATGATTCTTCCCAGTAAGAGAGGCTGTA	1238
	GGAGGAAC**G**CTCTATCG	1239
	CGATAGAG**C**GTTCCTCC	1240

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Arg117Pro CGC to CCC	TACAGCCTCTCTTACTGGGAAGAATCATAGCTTCCTATGACC CGGATAACAAGGAGGAAC**G**CTCTATCGCGATTTATCTAGGCA TAGGCTTATGCCTTCTCTTTATTGTGAGGACACTGCT	1241
	AGCAGTGTCCTCACAATAAAGAGAAGGCATAAGCCTATGCCT AGATAAATCGCGATAGAG**C**GTTCCTCCTTGTTATCCGGGTCA TAGGAAGCTATGATTCTTCCCAGTAAGAGAGGCTGTA	1242
	GGAGGAAC**G**CTCTATCG	1243
	CGATAGAG**C**GTTCCTCC	1244
Cystic fibrosis Ala120Thr GCG-ACG	CTCTTACTGGGAAGAATCATAGCTTCCTATGACCCGGATAAC AAGGAGGAACGCTCTATC**G**CGATTTATCTAGGCATAGGCTTA TGCCTTCTCTTTATTGTGAGGACACTGCTCCTACACC	1245
	GGTGTAGGAGCAGTGTCCTCACAATAAAGAGAAGGCATAAG CCTATGCCTAGATAAATCG**C**GATAGAGCGTTCCTCCTTGTTA TCCGGGTCATAGGAAGCTATGATTCTTCCCAGTAAGAG	1246
	GCTCTATC**G**CGATTTAT	1247
	ATAAATCG**C**GATAGAGC	1248
Cystic fibrosis Tyr122Term TAT to TAA	GGGAAGAATCATAGCTTCCTATGACCCGGATAACAAGGAGGA ACGCTCTATCGCGATTTA**T**CTAGGCATAGGCTTATGCCTTCT CTTTATTGTGAGGACACTGCTCCTACACCCAGCCATT	1249
	AATGGCTGGGTGTAGGAGCAGTGTCCTCACAATAAAGAGAA GGCATAAGCCTATGCCTAG**A**TAAATCGCGATAGAGCGTTCCT CCTTGTTATCCGGGTCATAGGAAGCTATGATTCTTCCC	1250
	GCGATTTA**T**CTAGGCAT	1251
	ATGCCTAG**A**TAAATCGC	1252
Cystic fibrosis Gly126Asp GGC-GAC	TAGCTTCCTATGACCCGGATAACAAGGAGGAACGCTCTATCG CGATTTATCTAGGCATAG**G**CTTATGCCTTCTCTTTATTGTGAG GACACTGCTCCTACACCCAGCCATTTTTGGCCTTCA	1253
	TGAAGGCCAAAAATGGCTGGGTGTAGGAGCAGTGTCCTCAC AATAAAGAGAAGGCATAAG**C**CTATGCCTAGATAAATCGCGAT AGAGCGTTCCTCCTTGTTATCCGGGTCATAGGAAGCTA	1254
	AGGCATAG**G**CTTATGCC	1255
	GGCATAAG**C**CTATGCCT	1256

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis His139Arg CAC to CGC	TCGCGATTTATCTAGGCATAGGCTTATGCCTTCTCTTTATTGTGAGGACACTGCTCCTAC**A**CCCAGCCATTTTTGGCCTTCATCACATTGGAATGCAGATGAGAATAGCTATGTTTAGTTT	1257
	AAACTAAACATAGCTATTCTCATCTGCATTCCAATGTGATGAAGGCCAAAAATGGCTGGG**T**GTAGGAGCAGTGTCCTCACAATAAAGAGAAGGCATAAGCCTATGCCTAGATAAATCGCGA	1258
	GCTCCTAC**A**CCCAGCCA	1259
	TGGCTGGG**T**GTAGGAGC	1260
Cystic fibrosis Ala141Asp GCC to GAC	TTTATCTAGGCATAGGCTTATGCCTTCTCTTTATTGTGAGGACACTGCTCCTACACCCAG**C**CATTTTTGGCCTTCATCACATTGGAATGCAGATGAGAATAGCTATGTTTAGTTTGATTTA	1261
	TAAATCAAACTAAACATAGCTATTCTCATCTGCATTCCAATGTGATGAAGGCCAAAAATG**G**CTGGGTGTAGGAGCAGTGTCCTCACAATAAAGAGAAGGCATAAGCCTATGCCTAGATAAA	1262
	ACACCCAG**C**CATTTTTG	1263
	CAAAAATG**G**CTGGGTGT	1264
Cystic fibrosis Ile148Thr ATT to ACT	GCCTTCTCTTTATTGTGAGGACACTGCTCCTACACCCAGCCATTTTTGGCCTTCATCACA**T**TGGAATGCAGATGAGAATAGCTATGTTTAGTTTGATTTATAAGAAGGTAATACTTCCTTG	1265
	CAAGGAAGTATTACCTTCTTATAAATCAAACTAAACATAGCTATTCTCATCTGCATTCCA**A**TGTGATGAAGGCCAAAAATGGCTGGGTGTAGGAGCAGTGTCCTCACAATAAAGAGAAGGC	1266
	TCATCACA**T**TGGAATGC	1267
	GCATTCCA**A**TGTGATGA	1268
Cystic fibrosis Gly149Arg GGA to AGA	CTTCTCTTTATTGTGAGGACACTGCTCCTACACCCAGCCATTTTTGGCCTTCATCACATT**G**GAATGCAGATGAGAATAGCTATGTTTAGTTTGATTTATAAGAAGGTAATACTTCCTTGCA	1269
	TGCAAGGAAGTATTACCTTCTTATAAATCAAACTAAACATAGCTATTCTCATCTGCATTC**C**AATGTGATGAAGGCCAAAAATGGCTGGGTGTAGGAGCAGTGTCCTCACAATAAAGAGAAG	1270
	ATCACATT**G**GAATGCAG	1271
	CTGCATTC**C**AATGTGAT	1272

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Gln151Term CAG to TAG	TTTATTGTGAGGACACTGCTCCTACACCCAGCCATTTTTGGC CTTCATCACATTGGAATG**C**AGATGAGAATAGCTATGTTTAGTT TGATTTATAAGAAGGTAATACTTCCTTGCACAGGCC	1273
	GGCCTGTGCAAGGAAGTATTACCTTCTTATAAATCAAACTAAA CATAGCTATTCTCATCT**G**CATTCCAATGTGATGAAGGCCAAAA ATGGCTGGGTGTAGGAGCAGTGTCCTCACAATAAA	1274
	TTGGAATG**C**AGATGAGA	1275
	TCTCATCT**G**CATTCCAA	1276
Cystic fibrosis Lys166Glu AAG-GAG	AATATATTTGTATTTTGTTTGTTGAAATTATCTAACTTTCCATTT TTCTTTTAGACTTTA**A**AGCTGTCAAGCCGTGTTCTAGATAAAA TAAGTATTGGACAACTTGTTAGTCTCCTTTCCA	1277
	TGGAAAGGAGACTAACAAGTTGTCCAATACTTATTTTATCTAG AACACGGCTTGACAGCT**T**TAAAGTCTAAAAGAAAAATGGAAA GTTAGATAATTTCAACAAACAAAATACAAATATATT	1278
	AGACTTTA**A**AGCTGTCA	1279
	TGACAGCT**T**TAAAGTCT	1280
Cystic fibrosis Ile175Val ATA-GTA	TTATCTAACTTTCCATTTTTCTTTTAGACTTTAAAGCTGTCAAG CCGTGTTCTAGATAAA**A**TAAGTATTGGACAACTTGTTAGTCTC CTTTCCAACAACCTGAACAAATTTGATGAAGTAT	1281
	ATACTTCATCAAATTTGTTCAGGTTGTTGGAAAGGAGACTAAC AAGTTGTCCAATACTTA**T**TTTATCTAGAACACGGCTTGACAGC TTTAAAGTCTAAAAGAAAAATGGAAAGTTAGATAA	1282
	TAGATAAA**A**TAAGTATT	1283
	AATACTTA**T**TTTATCTA	1284
Cystic fibrosis Gly178Arg GGA to AGA	TTTCCATTTTTCTTTTAGACTTTAAAGCTGTCAAGCCGTGTTCT AGATAAAATAAGTATT**G**GACAACTTGTTAGTCTCCTTTCCAAC AACCTGAACAAATTTGATGAAGTATGTACCTATT	1285
	AATAGGTACATACTTCATCAAATTTGTTCAGGTTGTTGGAAAG GAGACTAACAAGTTGTC**C**AATACTTATTTTATCTAGAACACGG CTTGACAGCTTTAAAGTCTAAAAGAAAAATGGAAA	1286
	TAAGTATT**G**GACAACTT	1287
	AAGTTGTC**C**AATACTTA	1288
Cystic fibrosis His199Gln CAT to CAG	AAGATACAATGACACCTGTTTTTGCTGTGCTTTTATTTTCCAG GGACTTGCATTGGCACA**T**TTCGTGTGGATCGCTCCTTTGCAA GTGGCACTCCTCATGGGGCTAATCTGGGAGTTGTTA	1289

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TAACAACTCCCAGATTAGCCCCATGAGGAGTGCCACTTGCAA AGGAGCGATCCACACGAA**A**TGTGCCAATGCAAGTCCCTGGA AAATAAAAGCACAGCAAAAACAGGTGTCATTGTATCTT	1290
	TTGGCACA**T**TTCGTGTG	1291
	CACACGAA**A**TGTGCCAA	1292
Cystic fibrosis His199Tyr CAT to TAT	GGAAGATACAATGACACCTGTTTTTGCTGTGCTTTTATTTTCC AGGGACTTGCATTGGCA**C**ATTTCGTGTGGATCGCTCCTTTGC AAGTGGCACTCCTCATGGGGCTAATCTGGGAGTTGT	1293
	ACAACTCCCAGATTAGCCCCATGAGGAGTGCCACTTGCAAAG GAGCGATCCACACGAAAT**G**TGCCAATGCAAGTCCCTGGAAA ATAAAAGCACAGCAAAAACAGGTGTCATTGTATCTTCC	1294
	CATTGGCA**C**ATTTCGTG	1295
	CACGAAAT**G**TGCCAATG	1296
Cystic fibrosis Pro205Ser CCT to TCT	TGTTTTTGCTGTGCTTTTATTTTCCAGGGACTTGCATTGGCAC ATTTCGTGTGGATCGCT**C**CTTTGCAAGTGGCACTCCTCATGG GGCTAATCTGGGAGTTGTTACAGGCGTCTGCCTTCT	1297
	AGAAGGCAGACGCCTGTAACAACTCCCAGATTAGCCCCATG AGGAGTGCCACTTGCAAAG**G**AGCGATCCACACGAAATGTGC CAATGCAAGTCCCTGGAAAATAAAAGCACAGCAAAAACA	1298
	GGATCGCT**C**CTTTGCAA	1299
	TTGCAAAG**G**AGCGATCC	1300
Cystic fibrosis Leu206Trp TTG to TGG	TTTGCTGTGCTTTTATTTTCCAGGGACTTGCATTGGCACATTT CGTGTGGATCGCTCCTT**T**GCAAGTGGCACTCCTCATGGGGC TAATCTGGGAGTTGTTACAGGCGTCTGCCTTCTGTGG	1301
	CCACAGAAGGCAGACGCCTGTAACAACTCCCAGATTAGCCC CATGAGGAGTGCCACTTGC**A**AAGGAGCGATCCACACGAAAT GTGCCAATGCAAGTCCCTGGAAAATAAAAGCACAGCAAA	1302
	CGCTCCTT**T**GCAAGTGG	1303
	CCACTTGC**A**AAGGAGCG	1304
Cystic fibrosis Gln220Term CAG to TAG	TTCGTGTGGATCGCTCCTTTGCAAGTGGCACTCCTCATGGG GCTAATCTGGGAGTTGTTA**C**AGGCGTCTGCCTTCTGTGGACT TGGTTTCCTGATAGTCCTTGCCCTTTTTCAGGCTGGGC	1305
	GCCCAGCCTGAAAAAGGGCAAGGACTATCAGGAAACCAAGT CCACAGAAGGCAGACGCCT**G**TAACAACTCCCAGATTAGCCC CATGAGGAGTGCCACTTGCAAAGGAGCGATCCACACGAA	1306

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGTTGTTA**C**AGGCGTCT	1307
	AGACGCCT**G**TAACAACT	1308
Cystic fibrosis Cys225Arg TGT-CGT	CCTTTGCAAGTGGCACTCCTCATGGGGCTAATCTGGGAGTT GTTACAGGCGTCTGCCTTC**T**GTGGACTTGGTTTCCTGATAGT CCTTGCCCTTTTTCAGGCTGGGCTAGGGAGAATGATGA	1309
	TCATCATTCTCCCTAGCCCAGCCTGAAAAAGGGCAAGGACTA TCAGGAAACCAAGTCCAC**A**GAAGGCAGACGCCTGTAACAAC TCCCAGATTAGCCCCATGAGGAGTGCCACTTGCAAAGG	1310
	CTGCCTTC**T**GTGGACTT	1311
	AAGTCCAC**A**GAAGGCAG	1312
Cystic fibrosis Val232Asp GTC to GAC	TGGGGCTAATCTGGGAGTTGTTACAGGCGTCTGCCTTCTGT GGACTTGGTTTCCTGATAG**T**CCTTGCCCTTTTTCAGGCTGGG CTAGGGAGAATGATGATGAAGTACAGGTAGCAACCTAT	1313
	ATAGGTTGCTACCTGTACTTCATCATCATTCTCCCTAGCCCA GCCTGAAAAAGGGCAAGG**A**CTATCAGGAAACCAAGTCCACA GAAGGCAGACGCCTGTAACAACTCCCAGATTAGCCCCA	1314
	CCTGATAG**T**CCTTGCCC	1315
	GGGCAAGG**A**CTATCAGG	1316
Cystic fibrosis Gly239Arg GGG to AGG	GTTACAGGCGTCTGCCTTCTGTGGACTTGGTTTCCTGATAGT CCTTGCCCTTTTTCAGGC**T**GGGCTAGGGAGAATGATGATGAA GTACAGGTAGCAACCTATTTTCATAACTTGAAAGTTT	1317
	AAACTTTCAAGTTATGAAAATAGGTTGCTACCTGTACTTCATC ATCATTCTCCCTAGCCC**A**GCCTGAAAAAGGGCAAGGACTATC AGGAAACCAAGTCCACAGAAGGCAGACGCCTGTAAC	1318
	TTTCAGGC**T**GGGCTAGG	1319
	CCTAGCCC**A**GCCTGAAA	1320

EXAMPLE 10
Cyclin-dependent kinase inhibitor 2A - CDKN2A

The human CDKN2A gene was also designated MTS-1 for multiple tumor suppressor-1 and has been implicated in multiple cancers including, for example, malignant melanoma. Malignant melanoma is a cutaneous neoplasm of melanocytes. Melanomas generally have features of asymmetry, irregular border, variegated color, and diameter greater than 6 mm. The precise cause of melanoma is

unknown, but sunlight and heredity are risk factors. Melanoma has been increasing during the past few decades.

The CDKN2A gene has been found to be homozygously deleted at high frequency in cell lines derived from tumors of lung, breast, brain, bone, skin, bladder, kidney, ovary, and lymphocyte. Melanoma cell lines carried at least one copy of CDKN2A in combination with a deleted allele. Melanoma cell lines that carried at least 1 copy of CDKN2A frequently showed nonsense, missense, or frameshift mutations in the gene. Thus, CDKN2A may rival p53 (see Example 5) in the universality of its involvement in tumorigenesis. The attached table discloses the correcting oligonucleotide base sequences for the CDKN2A oligonucleotides of the invention.

Table 17
CDKN2A Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Melanoma Trp15Term TGG-TAG	GGGCGGCGGGGAGCAGCATGGAGCCGGCGGCGGGGAGCAG CATGGAGCCTTCGGCTGACT**G**GCTGGCCACGGCCGCGGCCC GGGGTCGGGTAGAGGAGGTGCGGGCGCTGCTGGAGGCGGG	1321
	CCCGCCTCCAGCAGCGCCCGCACCTCCTCTACCCGACCCCG GGCCGCGGCCGTGGCCAGC**C**AGTCAGCCGAAGGCTCCATGC TGCTCCCCGCCGCCGGCTCCATGCTGCTCCCCGCCGCCC	1322
	GGCTGACT**G**GCTGGCCA	1323
	TGGCCAGC**C**AGTCAGCC	1324
Melanoma Leu16Pro CTG-CCG	CGGCGGGGAGCAGCATGGAGCCGGCGGCGGGGAGCAGCAT GGAGCCTTCGGCTGACTGGC**T**GGCCACGGCCGCGGCCCGG GGTCGGGTAGAGGAGGTGCGGGCGCTGCTGGAGGCGGGGG C	1325
	GCCCCCGCCTCCAGCAGCGCCCGCACCTCCTCTACCCGACC CCGGGCCGCGGCCGTGGCC**A**GCCAGTCAGCCGAAGGCTCC ATGCTGCTCCCCGCCGCCGGCTCCATGCTGCTCCCCGCCG	1326
	TGACTGGC**T**GGCCACGG	1327
	CCGTGGCC**A**GCCAGTCA	1328
Melanoma Gly23Asp GGT-GAT	CGGCGGCGGGGAGCAGCATGGAGCCTTCGGCTGACTGGCTG GCCACGGCCGCGGCCCGGG**G**TCGGGTAGAGGAGGTGCGGG CGCTGCTGGAGGCGGGGGCGCTGCCCAACGCACCGAATAG	1329
	CTATTCGGTGCGTTGGGCAGCGCCCCCGCCTCCAGCAGCGC CCGCACCTCCTCTACCCGA**C**CCCGGGCCGCGGCCGTGGCCA GCCAGTCAGCCGAAGGCTCCATGCTGCTCCCCGCCGCCG	1330
	GGCCCGGG**G**TCGGGTAG	1331

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CTACCCGA**C**CCCGGGCC	1332
Melanoma Arg24Pro CGG-CCG	CGGCGGGGAGCAGCATGGAGCCTTCGGCTGACTGGCTGGCC ACGGCCGCGGCCCGGGGTC**G**GGTAGAGGAGGTGCGGGCGC TGCTGGAGGCGGGGGCGCTGCCCAACGCACCGAATAGTTA	1333
	TAACTATTCGGTGCGTTGGGCAGCGCCCCCGCCTCCAGCAGC GCCCGCACCTCCTCTACC**C**GACCCCGGGCCGCGGCCGTGGC CAGCCAGTCAGCCGAAGGCTCCATGCTGCTCCCCGCCG	1334
	CCGGGGTC**G**GGTAGAGG	1335
	CCTCTACC**C**GACCCCGG	1336
Melanoma Leu32Pro CTG-CCG	CGGCTGACTGGCTGGCCACGGCCGCGGCCCGGGGTCGGGT AGAGGAGGTGCGGGCGCTGC**T**GGAGGCGGGGGCGCTGCCC AACGCACCGAATAGTTACGGTCGGAGGCCGATCCAGGTGGG	1337
	CCCACCTGGATCGGCCTCCGACCGTAACTATTCGGTGCGTTG GGCAGCGCCCCCGCCTCC**A**GCAGCGCCCGCACCTCCTCTAC CCGACCCCGGGCCGCGGCCGTGGCCAGCCAGTCAGCCG	1338
	GGCGCTGC**T**GGAGGCGG	1339
	CCGCCTCC**A**GCAGCGCC	1340
Melanoma Gly35Ala GGG-GCG	GGCTGGCCACGGCCGCGGCCCGGGGTCGGGTAGAGGAGGT GCGGGCGCTGCTGGAGGCGG**G**GGCGCTGCCCAACGCACCG AATAGTTACGGTCGGAGGCCGATCCAGGTGGGTAGAGGGTC	1341
	GACCCTCTACCCACCTGGATCGGCCTCCGACCGTAACTATTC GGTGCGTTGGGCAGCGCC**C**CCGCCTCCAGCAGCGCCCGCAC CTCCTCTACCCGACCCCGGGCCGCGGCCGTGGCCAGCC	1342
	GGAGGCGG**G**GGCGCTGC	1343
	GCAGCGCC**C**CCGCCTCC	1344
Melanoma Tyr44Term TACg-TAA	GGTAGAGGAGGTGCGGGCGCTGCTGGAGGCGGGGGCGCTG CCCAACGCACCGAATAGTTA**C**GGTCGGAGGCCGATCCAGGTG GGTAGAGGGTCTGCAGCGGGAGCAGGGGATGGCGGGCGA	1345
	TCGCCCGCCATCCCCTGCTCCCGCTGCAGACCCTCTACCCAC CTGGATCGGCCTCCGACC**G**TAACTATTCGGTGCGTTGGGCAG CGCCCCCGCCTCCAGCAGCGCCCGCACCTCCTCTACC	1346
	AATAGTTA**C**GGTCGGAG	1347
	CTCCGACC**G**TAACTATT	1348
Melanoma Met53Ile ATGa-ATC	TCTCCCATACCTGCCCCCACCCTGGCTCTGACCACTCTGCTC TCTCTGGCAGGTCATGAT**G**ATGGGCAGCGCCCGCGTGGCGG AGCTGCTGCTGCTCCACGGCGCGGAGCCCAACTGCGCA	1349
	TGCGCAGTTGGGCTCCGCGCCGTGGAGCAGCAGCAGCTCCG CCACGCGGGCGCTGCCCAT**C**ATCATGACCTGCCAGAGAGAG CAGAGTGGTCAGAGCCAGGGTGGGGGCAGGTATGGGAGA	1350
	GTCATGAT**G**ATGGGCAG	1351

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CTGCCCAT**C**ATCATGAC	1352
Melanoma Met54Ile ATGg-ATT	CCCATACCTGCCCCCACCCTGGCTCTGACCACTCTGCTCTCT CTGGCAGGTCATGATGAT**G**GGCAGCGCCCGCGTGGCGGAGC TGCTGCTGCTCCACGGCGCGGAGCCCAACTGCGCAGAC	1353
	GTCTGCGCAGTTGGGCTCCGCGCCGTGGAGCAGCAGCAGCT CCGCCACGCGGGCGCTGCC**C**ATCATCATGACCTGCCAGAGA GAGCAGAGTGGTCAGAGCCAGGGTGGGGGCAGGTATGGG	1354
	ATGATGAT**G**GGCAGCGC	1355
	GCGCTGCC**C**ATCATCAT	1356
Melanoma Ser56Ile AGC-ATC	GCCGGCCCCCACCCTGGCTCTGACCATTCTGTTCTCTCTGGC AGGTCATGATGATGGGCA**G**CGCCCGAGTGGCGGAGCTGCTG CTGCTCCACGGCGCGGAGCCCAACTGCGCCGACCCCGC	1357
	GCGGGGTCGGCGCAGTTGGGCTCCGCGCCGTGGAGCAGCA GCAGCTCCGCCACTCGGGCG**C**TGCCCATCATCATGACCTGCC AGAGAGAACAGAATGGTCAGAGCCAGGGTGGGGGCCGGC	1358
	GATGGGCA**G**CGCCCGAG	1359
	CTCGGGCG**C**TGCCCATC	1360
Melanoma Ala57Val GCC-GTC	GGCCCCCACCCTGGCTCTGACCATTCTGTTCTCTCTGGCAGG TCATGATGATGGGCAGCG**C**CCGAGTGGCGGAGCTGCTGCTG CTCCACGGCGCGGAGCCCAACTGCGCCGACCCCGCCAC	1361
	GTGGCGGGGTCGGCGCAGTTGGGCTCCGCGCCGTGGAGCA GCAGCAGCTCCGCCACTCGG**G**CGCTGCCCATCATCATGACCT GCCAGAGAGAACAGAATGGTCAGAGCCAGGGTGGGGGCC	1362
	GGGCAGCG**C**CCGAGTGG	1363
	CCACTCGG**G**CGCTGCCC	1364
Melanoma Arg58Term cCGA-TGA	CCCCCACCCTGGCTCTGACCATTCTGTTCTCTCTGGCAGGTC ATGATGATGGGCAGCGCC**C**GAGTGGCGGAGCTGCTGCTGCT CCACGGCGCGGAGCCCAACTGCGCCGACCCCGCCACTC	1365
	GAGTGGCGGGGTCGGCGCAGTTGGGCTCCGCGCCGTGGAG CAGCAGCAGCTCCGCCACTC**G**GGCGCTGCCCATCATCATGAC CTGCCAGAGAGAACAGAATGGTCAGAGCCAGGGTGGGGG	1366
	GCAGCGCC**C**GAGTGGCG	1367
	CGCCACTC**G**GGCGCTGC	1368
Melanoma Val59Gly GTG-GGG	CACCCTGGCTCTGACCATTCTGTTCTCTCTGGCAGGTCATGAT GATGGGCAGCGCCCGAG**T**GGCGGAGCTGCTGCTGCTCCACG GCGCGGAGCCCAACTGCGCCGACCCCGCCACTCTCAC	1369
	GTGAGAGTGGCGGGGTCGGCGCAGTTGGGCTCCGCGCCGTG GAGCAGCAGCAGCTCCGCC**A**CTCGGGCGCTGCCCATCATCA TGACCTGCCAGAGAGAACAGAATGGTCAGAGCCAGGGTG	1370
	CGCCCGAG**T**GGCGGAGC	1371

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GCTCCGCC**A**CTCGGGCG	1372
Melanoma Leu62Pro CTG-CCG	TCTGACCACTCTGCTCTCTCTGGCAGGTCATGATGATGGGCA GCGCCCGCGTGGCGGAGC**T**GCTGCTGCTCCACGGCGCGGA GCCCAACTGCGCAGACCCTGCCACTCTCACCCGACCGGT	1373
	ACCGGTCGGGTGAGAGTGGCAGGGTCTGCGCAGTTGGGCTC CGCGCCGTGGAGCAGCAGC**A**GCTCCGCCACGCGGGCGCTG CCCATCATCATGACCTGCCAGAGAGAGCAGAGTGGTCAGA	1374
	GGCGGAGC**T**GCTGCTGC	1375
	GCAGCAGC**A**GCTCCGCC	1376
Melanoma Ala68Val GCG-GTG	TCTGGCAGGTCATGATGATGGGCAGCGCCCGCGTGGCGGAG CTGCTGCTGCTCCACGGCG**C**GGAGCCCAACTGCGCAGACCC TGCCACTCTCACCCGACCGGTGCATGATGCTGCCCGGGA	1377
	TCCCGGGCAGCATCATGCACCGGTCGGGTGAGAGTGGCAGG GTCTGCGCAGTTGGGCTCC**G**CGCCGTGGAGCAGCAGCAGCT CCGCCACGCGGGCGCTGCCCATCATCATGACCTGCCAGA	1378
	CCACGGCG**C**GGAGCCCA	1379
	TGGGCTCC**G**CGCCGTGG	1380
Melanoma Asn71Lys AACt-AAA	CATGATGATGGGCAGCGCCCGAGTGGCGGAGCTGCTGCTGC TCCACGGCGCGGAGCCCAA**C**TGCGCCGACCCCGCCACTCTC ACCCGACCCGTGCACGACGCTGCCCGGGAGGGCTTCCTG	1381
	CAGGAAGCCCTCCCGGGCAGCGTCGTGCACGGGTCGGGTGA GAGTGGCGGGGTCGGCGCA**G**TTGGGCTCCGCGCCGTGGAG CAGCAGCAGCTCCGCCACTCGGGCGCTGCCCATCATCATG	1382
	GAGCCCAA**C**TGCGCCGA	1383
	TCGGCGCA**G**TTGGGCTC	1384
Melanoma Asn71Ser AAC-AGC	TCATGATGATGGGCAGCGCCCGAGTGGCGGAGCTGCTGCTG CTCCACGGCGCGGAGCCCA**A**CTGCGCCGACCCCGCCACTCT CACCCGACCCGTGCACGACGCTGCCCGGGAGGGCTTCCT	1385
	AGGAAGCCCTCCCGGGCAGCGTCGTGCACGGGTCGGGTGAG AGTGGCGGGGTCGGCGCAG**T**TGGGCTCCGCGCCGTGGAGCA GCAGCAGCTCCGCCACTCGGGCGCTGCCCATCATCATGA	1386
	GGAGCCCA**A**CTGCGCCG	1387
	CGGCGCAG**T**TGGGCTCC	1388
Melanoma Pro81Leu CCC-CTC	AGCTGCTGCTGCTCCACGGCGCGGAGCCCAACTGCGCCGAC CCCGCCACTCTCACCCGAC**C**CGTGCACGACGCTGCCCGGGA GGGCTTCCTGGACACGCTGGTGGTGCTGCACCGGGCCGG	1389
	CCGGCCCGGTGCAGCACCACCAGCGTGTCCAGGAAGCCCTC CCGGGCAGCGTCGTGCACG**G**GTCGGGTGAGAGTGGCGGGG TCGGCGCAGTTGGGCTCCGCGCCGTGGAGCAGCAGCAGCT	1390
	CACCCGAC**C**CGTGCACG	1391

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Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CGTGCACG**G**GTCGGGTG	1392
Melanoma Asp84Tyr cGAC-TAC	CTGCTCCACGGCGCGGAGCCCAACTGCGCCGACCCCGCCAC TCTCACCCGACCCGTGCAC**G**ACGCTGCCCGGGAGGGCTTCC TGGACACGCTGGTGGTGCTGCACCGGGCCGGGGCGCGGC	1393
	GCCGCGCCCCGGCCCGGTGCAGCACCACCAGCGTGTCCAGG AAGCCCTCCCGGGCAGCGT**C**GTGCACGGGTCGGGTGAGAGT GGCGGGGTCGGCGCAGTTGGGCTCCGCGCCGTGGAGCAG	1394
	CCGTGCAC**G**ACGCTGCC	1395
	GGCAGCGT**C**GTGCACGG	1396
Melanoma Ala85Thr cGCT-ACT	CTCCACGGCGCGGAGCCCAACTGCGCCGACCCCGCCACTCT CACCCGACCCGTGCACGAC**G**CTGCCCGGGAGGGCTTCCTGG ACACGCTGGTGGTGCTGCACCGGGCCGGGGCGCGGCTGG	1397
	CCAGCCGCGCCCCGGCCCGGTGCAGCACCACCAGCGTGTCC AGGAAGCCCTCCCGGGCAG**C**GTCGTGCACGGGTCGGGTGAG AGTGGCGGGGTCGGCGCAGTTGGGCTCCGCGCCGTGGAG	1398
	TGCACGAC**G**CTGCCCGG	1399
	CCGGGCAG**C**GTCGTGCA	1400
Melanoma Arg87Pro CGG-CCG	GCGCGGAGCCCAACTGCGCCGACCCCGCCACTCTCACCCGA CCCGTGCACGACGCTGCCC**G**GGAGGGCTTCCTGGACACGCT GGTGGTGCTGCACCGGGCCGGGGCGCGGCTGGACGTGCG	1401
	CGCACGTCCAGCCGCGCCCCGGCCCGGTGCAGCACCACCAG CGTGTCCAGGAAGCCCTCC**C**GGGCAGCGTCGTGCACGGGTC GGGTGAGAGTGGCGGGGTCGGCGCAGTTGGGCTCCGCGC	1402
	CGCTGCCC**G**GGAGGGCT	1403
	AGCCCTCC**C**GGGCAGCG	1404
Melanoma Arg87Trp cCGG-TGG	GGCGCGGAGCCCAACTGCGCCGACCCCGCCACTCTCACCCG ACCCGTGCACGACGCTGCC**C**GGGAGGGCTTCCTGGACACGC TGGTGGTGCTGCACCGGGCCGGGGCGCGGCTGGACGTGC	1405
	GCACGTCCAGCCGCGCCCCGGCCCGGTGCAGCACCACCAGC GTGTCCAGGAAGCCCTCCC**G**GGCAGCGTCGTGCACGGGTCG GGTGAGAGTGGCGGGGTCGGCGCAGTTGGGCTCCGCGCC	1406
	ACGCTGCC**C**GGGAGGGC	1407
	GCCCTCCC**G**GGCAGCGT	1408
Melanoma Leu97Arg CTG-CGG	CTCTCACCCGACCGGTGCATGATGCTGCCCGGGAGGGCTTC CTGGACACGCTGGTGGTGC**T**GCACCGGGCCGGGGCGCGGCT GGACGTGCGCGATGCCTGGGGTCGTCTGCCCGTGGACTT	1409
	AAGTCCACGGGCAGACGACCCCAGGCATCGCGCACGTCCAG CCGCGCCCCGGCCCGGTGC**A**GCACCACCAGCGTGTCCAGGA AGCCCTCCCGGGCAGCATCATGCACCGGTCGGGTGAGAG	1410
	GGTGGTGC**T**GCACCGGG	1411

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CCCGGTGC**A**GCACCACC	1412
Melanoma Arg99Pro CGG-CCG	CCCGACCGGTGCATGATGCTGCCCGGGAGGGCTTCCTGGAC ACGCTGGTGGTGCTGCACC**G**GGCCGGGGCGCGGCTGGACG TGCGCGATGCCTGGGGTCGTCTGCCCGTGGACTTGGCCGA	1413
	TCGGCCAAGTCCACGGGCAGACGACCCCAGGCATCGCGCAC GTCCAGCCGCGCCCCGGCC**C**GGTGCAGCACCACCAGCGTGT CCAGGAAGCCCTCCCGGGCAGCATCATGCACCGGTCGGG	1414
	GCTGCACC**G**GGCCGGGG	1415
	CCCCGGCC**C**GGTGCAGC	1416
Melanoma Gly101Trp cGGG-TGG	CCGGTGCATGATGCTGCCCGGGAGGGCTTCCTGGACACGCT GGTGGTGCTGCACCGGGCC**G**GGGCGCGGCTGGACGTGCGC GATGCCTGGGGTCGTCTGCCCGTGGACTTGGCCGAGGAGC	1417
	GCTCCTCGGCCAAGTCCACGGGCAGACGACCCCAGGCATCG CGCACGTCCAGCCGCGCCC**C**GGCCCGGTGCAGCACCACCAG CGTGTCCAGGAAGCCCTCCCGGGCAGCATCATGCACCGG	1418
	ACCGGGCC**G**GGGCGCGG	1419
	CCGCGCCC**C**GGCCCGGT	1420
Melanoma Arg107Cys gCGC-TGC	CGGGAGGGCTTCCTGGACACGCTGGTGGTGCTGCACCGGGC CGGGGCGCGGCTGGACGTG**C**GCGATGCCTGGGGTCGTCTGC CCGTGGACTTGGCCGAGGAGCGGGGCCACCGCGACGTTG	1421
	CAACGTCGCGGTGGCCCCGCTCCTCGGCCAAGTCCACGGGC AGACGACCCCAGGCATCGC**G**CACGTCCAGCCGCGCCCCGGC CCGGTGCAGCACCACCAGCGTGTCCAGGAAGCCCTCCCG	1422
	TGGACGTG**C**GCGATGCC	1423
	GGCATCGC**G**CACGTCCA	1424
Melanoma Ala118Thr gGCT-ACT	CACCGGGCCGGGGCGCGGCTGGACGTGCGCGATGCCTGGG GCCGTCTGCCCGTGGACCTG**G**CTGAGGAGCTGGGCCATCGC GATGTCGCACGGTACCTGCGCGCGGCTGCGGGGGGCACCA	1425
	TGGTGCCCCCCGCAGCCGCGCGCAGGTACCGTGCGACATCG CGATGGCCCAGCTCCTCAG**C**CAGGTCCACGGGCAGACGGCC CCAGGCATCGCGCACGTCCAGCCGCGCCCCGGCCCGGTG	1426
	TGGACCTG**G**CTGAGGAG	1427
	CTCCTCAG**C**CAGGTCCA	1428
Melanoma Val126Asp GTC-GAC	TGCGCGATGCCTGGGGCCGTCTGCCCGTGGACCTGGCTGAG GAGCTGGGCCATCGCGATG**T**CGCACGGTACCTGCGCGCGGC TGCGGGGGGCACCAGAGGCAGTAACCATGCCCGCATAGA	1429
	TCTATGCGGGCATGGTTACTGCCTCTGGTGCCCCCCGCAGCC GCGCGCAGGTACCGTGCG**A**CATCGCGATGGCCCACC[illegible]CCTC AGCCAGGTCCACGGGCAGACGGCCCCAGGCATCGCGCA	1430
	TCGCGATG**T**CGCACGGT	1431

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ACCGTGCG<u>A</u>CATCGCGA	1432

EXAMPLE 11
<u>Adenomatous polyposis of the colon - APC</u>

Adenomatous polyposis of the colon is characterized by adenomatous polyps of the colon and rectum; in extreme cases the bowel is carpeted with a myriad of polyps. This is a viciously premalignant disease with one or more polyps progressing through dysplasia to malignancy in untreated gene carriers with a median age at diagnosis of 40 years.

Mutations in the APC gene are an initiating event for both familial and sporadic colorectal tumorigenesis and many alleles of the APC gene have been identified. Carcinoma may arise at any age from late childhood through the seventh decade with presenting features including, for example, weight loss and inanition, bowel obstruction, or bloody diarrhea. Cases of new mutation still present in these ways but in areas with well organized registers most other gene carriers are detected. The attached table discloses the correcting oligonucleotide base sequences for the APC oligonucleotides of the invention.

Table 18
APC Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenomatous polyposis coli Arg121Term AGA-TGA	GGATCTGTATCAAGCCGTTCTGGAGAGTGCAGTCCTGTTCCT ATGGGTTCATTTCCAAGA**A**GAGGGTTTGTAAATGGAAGCAGA GAAAGTACTGGATATTTAGAAGAACTTGAGAAAGAGA	1433
	TCTCTTTCTCAAGTTCTTCTAAATATCCAGTACTTTCTCTGCTT CCATTTACAAACCCTC**T**TCTTGGAAATGAACCCATAGGAACAG GACTGCACTCTCCAGAACGGCTTGATACAGATCC	1434
	TTCCAAGA**A**GAGGGTTT	1435
	AAACCCTC**T**TCTTGGAA	1436
Adenomatous polyposis coli Trp157Term TGG-TAG	AAAAAAAAAATAGGTCATTGCTTCTTGCTGATCTTGACAAAGAA GAAAAGGAAAAAGACT**G**GTATTACGCTCAACTTCAGAATCTCA CTAAAAGAATAGATAGTCTTCCTTTAACTGAAAA	1437
	TTTTCAGTTAAAGGAAGACTATCTATTCTTTTAGTGAGATTCTG AAGTTGAGCGTAATAC**C**AGTCTTTTTCCTTTTCTTCTTTGTCAA GATCAGCAAGAAGCAATGACCTATTTTTTTTTT	1438
	AAAAGACT**G**GTATTACG	1439
	CGTAATAC**C**AGTCTTTT	1440
Adenomatous polyposis coli Tyr159Term TAC-TAG	AAATAGGTCATTGCTTCTTGCTGATCTTGACAAAGAAGAAAAG GAAAAAGACTGGTATTA**C**GCTCAACTTCAGAATCTCACTAAAA GAATAGATAGTCTTCCTTTAACTGAAAATGTAAGT	1441
	ACTTACATTTTCAGTTAAAGGAAGACTATCTATTCTTTTAGTGA GATTCTGAAGTTGAGC**G**TAATACCAGTCTTTTTCCTTTTCTTCT TTGTCAAGATCAGCAAGAAGCAATGACCTATTT	1442
	TGGTATTA**C**GCTCAACT	1443
	AGTTGAGC**G**TAATACCA	1444
Adenomatous polyposis coli Gln163Term CAG-TAG	TTGCTTCTTGCTGATCTTGACAAAGAAGAAAAGGAAAAAGACT GGTATTACGCTCAACTT**C**AGAATCTCACTAAAAGAATAGATAG TCTTCCTTTAACTGAAAATGTAAGTAACTGGCAGT	1445
	ACTGCCAGTTACTTACATTTTCAGTTAAAGGAAGACTATCTATT CTTTTAGTGAGATTCT**G**AAGTTGAGCGTAATACCAGTCTTTTTC CTTTTCTTCTTTGTCAAGATCAGCAAGAAGCAA	1446
	CTCAACTT**C**AGAATCTC	1447
	GAGATTCT**G**AAGTTGAG	1448
Adenomatous polyposis coli Arg168Term AGA-TGA	CTTGACAAAGAAGAAAAGGAAAAAGACTGGTATTACGCTCAAC TTCAGAATCTCACTAAA**A**GAATAGATAGTCTTCCTTTAACTGAA AATGTAAGTAACTGGCAGTACAACTTATTTGAAA	1449
	TTTCAAATAAGTTGTACTGCCAGTTACTTACATTTTCAGTTAAA GGAAGACTATCTATTC**T**TTTAGTGAGATTCTGAAGTTGAGCGT AATACCAGTCTTTTTCCTTTTCTTCTTTGTCAAG	1450

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TCACTAAA**A**GAATAGAT	1451
	ATCTATTC**T**TTTAGTGA	1452
Adenomatous polyposis coli Ser171Ile AGT-ATT	AAGAAAAGGAAAAAGACTGGTATTACGCTCAACTTCAGAATCTCACTAAAAGAATAGATA**G**TCTTCCTTTAACTGAAAATGTAAGTAACTGGCAGTACAACTTATTTGAAACTTTAATAAC	1453
	GTTATTAAAGTTTCAAATAAGTTGTACTGCCAGTTACTTACATTTTCAGTTAAAGGAAGA**C**TATCTATTCTTTTAGTGAGATTCTGAAGTTGAGCGTAATACCAGTCTTTTTCCTTTTCTT	1454
	AATAGATA**G**TCTTCCTT	1455
	AAGGAAGA**C**TATCTATT	1456
Adenomatous polyposis coli Gln181Term CAA-TAA	GATTAACGTAAATACAAGATATTGATACTTTTTTATTATTTGTGGTTTTAGTTTTCCTTA**C**AAACAGATATGACCAGAAGGCAATTGGAATATGAAGCAAGGCAAATCAGAGTTGCGATGG	1457
	CCATCGCAACTCTGATTTGCCTTGCTTCATATTCCAATTGCCTTCTGGTCATATCTGTTT**G**TAAGGAAAACTAAAACCACAAATAATAAAAAAGTATCAATATCTTGTATTTACGTTAATC	1458
	TTTCCTTA**C**AAACAGAT	1459
	ATCTGTTT**G**TAAGGAAA	1460
Adenomatous polyposis coli Glu190Term GAA-TAA	CTTTTTTATTATTTGTGGTTTTAGTTTTCCTTACAAACAGATATGACCAGAAGGCAATTG**G**AATATGAAGCAAGGCAAATCAGAGTTGCGATGGAAGAACAACTAGGTACCTGCCAGGATA	1461
	TATCCTGGCAGGTACCTAGTTGTTCTTCCATCGCAACTCTGATTTGCCTTGCTTCATATT**C**CAATTGCCTTCTGGTCATATCTGTTTGTAAGGAAAACTAAAACCACAAATAATAAAAAAG	1462
	GGCAATTG**G**AATATGAA	1463
	TTCATATT**C**CAATTGCC	1464
Adenomatous polyposis coli Gln208Term CAG-TAG	CAATTGGAATATGAAGCAAGGCAAATCAGAGTTGCGATGGAAGAACAACTAGGTACCTGC**C**AGGATATGGAAAAACGAGCACAGGTAAGTTACTTGTTTCTAAGTGATAAAACAGCGAAGA	1465
	TCTTCGCTGTTTTATCACTTAGAAACAAGTAACTTACCTGTGCTCGTTTTTCCATATCCT**G**GCAGGTACCTAGTTGTTCTTCCATCGCAACTCTGATTTGCCTTGCTTCATATTCCAATTG	1466
	GTACCTGC**C**AGGATATG	1467
	CATATCCT**G**GCAGGTAC	1468
Adenomatous polyposis coli Arg213Term CGA-TGA	GCAAGGCAAATCAGAGTTGCGATGGAAGAACAACTAGGTACCTGCCAGGATATGGAAAAA**C**GAGCACAGGTAAGTTACTTGTTTCTAAGTGATAAAACAGCGAAGAGCTATTAGGAATAAA	1469
	TTTATTCCTAATAGCTCTTCGCTGTTTTATCACTTAGAAACAAGTAACTTACCTGTGCTC**G**TTTTTCCATATCCTGGCAGGTACCTAGTTGTTCTTCCATCGCAACTCTGATTTGCCTTGC	1470
	TGGAAAAA**C**GAGCACAG	1471
	CTGTGCTC**G**TTTTTCCA	1472

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenomatous polyposis coli Arg232Term CGA-TGA	GTTTTATTTTAGCGAAGAATAGCCAGAATTCAGCAAATCGAAAAGGACATACTTCGTATA**C**GACAGCTTTTACAGTCCCAAGCAACAGAAGCAGAGGTTAGTAAATTGCCTTTCTTGTTTG	1473
	CAAACAAGAAAGGCAATTTACTAACCTCTGCTTCTGTTGCTTGGGACTGTAAAAGCTGTC**G**TATACGAAGTATGTCCTTTTCGATTTGCTGAATTCTGGCTATTCTTCGCTAAAATAAAAC	1474
	TTCGTATA**C**GACAGCTT	1475
	AAGCTGTC**G**TATACGAA	1476
Adenomatous polyposis coli Gln233Term CAG-TAG	TTATTTTAGCGAAGAATAGCCAGAATTCAGCAAATCGAAAAGGACATACTTCGTATACGA**C**AGCTTTTACAGTCCCAAGCAACAGAAGCAGAGGTTAGTAAATTGCCTTTCTTGTTTGTGG	1477
	CCACAAACAAGAAAGGCAATTTACTAACCTCTGCTTCTGTTGCTTGGGACTGTAAAAGCT**G**TCGTATACGAAGTATGTCCTTTTCGATTTGCTGAATTCTGGCTATTCTTCGCTAAAATAA	1478
	GTATACGA**C**AGCTTTTA	1479
	TAAAAGCT**G**TCGTATAC	1480
Adenomatous polyposis coli Gln247Term CAG-TAG	AGAAAGCCTACACCATTTTTGCATGTACTGATGTTAACTCCATCTTAACAGAGGTCATCT**C**AGAACAAGCATGAAACCGGCTCACATGATGCTGAGCGGCAGAATGAAGGTCAAGGAGTGG	1481
	CCACTCCTTGACCTTCATTCTGCCGCTCAGCATCATGTGAGCCGGTTTCATGCTTGTTCT**G**AGATGACCTCTGTTAAGATGGAGTTAACATCAGTACATGCAAAAATGGTGTAGGCTTTCT	1482
	GGTCATCT**C**AGAACAAG	1483
	CTTGTTCT**G**AGATGACC	1484
Adenomatous polyposis coli Gly267Term GGA-TGA	CAGAACAAGCATGAAACCGGCTCACATGATGCTGAGCGGCAGAATGAAGGTCAAGGAGTG**G**GAGAAATCAACATGGCAACTTCTGGTAATGGTCAGGTAAATAAATTATTTTATCATATTT	1485
	AAATATGATAAAATAATTTATTTACCTGACCATTACCAGAAGTTGCCATGTTGATTTCTC**C**CACTCCTTGACCTTCATTCTGCCGCTCAGCATCATGTGAGCCGGTTTCATGCTTGTTCTG	1486
	AAGGAGTG**G**GAGAAATC	1487
	GATTTCTC**C**CACTCCTT	1488
Adenomatous polyposis coli Glu443Term GAA-TAA	CTTCAAATAACAAAGCATTATGGTTTATGTTGATTTTATTTTTCAGTGCCAGCTCCTGTT**G**AACATCAGATCTGTCCTGCTGTGTGTGTTCTAATGAAACTTTCATTTGATGAAGAGCATA	1489
	TATGCTCTTCATCAAATGAAAGTTTCATTAGAACACACACAGCAGGACAGATCTGATGTT**C**AACAGGAGCTGGCACTGAAAAATAAAATCAACATAAACCATAATGCTTTGTTATTTGAAG	1490
	CTCCTGTT**G**AACATCAG	1491
	CTGATGTT**C**AACAGGAG	1492
Adenomatous polyposis coli SER457TER TCA-TAA	CAGTGCCAGCTCCTGTTGAACATCAGATCTGTCCTGCTGTGTGTGTTCTAATGAAACTTT**C**ATTTGATGAAGAGCATAGACATGCAATGAATGAACTAGGTAAGACAAAAATGTTTTTTAA	1493

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TTAAAAAACATTTTTGTCTTACCTAGTTCATTCATTGCATGTCTA TGCTCTTCATCAAAT**G**AAAGTTTCATTAGAACACACACAGCAG GACAGATCTGATGTTCAACAGGAGCTGGCACTG	1494
	GAAACTTT**C**ATTTGATG	1495
	CATCAAAT**G**AAAGTTTC	1496
Adenomatous polyposis coli Gln473Term CAG-TAG	AGTTGTTTTATTTTAGATGATTGTCTTTTTCCTCTTGCCCTTTTT AAATTAGGGGGACTA**C**AGGCCATTGCAGAATTATTGCAAGTG GACTGTGAAATGTACGGGCTTACTAATGACCACT	1497
	AGTGGTCATTAGTAAGCCCGTACATTTCACAGTCCACTTGCAA TAATTCTGCAATGGCCT**G**TAGTCCCCCTAATTTAAAAAGGGCA AGAGGAAAAAGACAATCATCTAAAATAAAACAACT	1498
	GGGGACTA**C**AGGCCATT	1499
	AATGGCCT**G**TAGTCCCC	1500
Adenomatous polyposis coli Tyr486Term TAC-TAG	TTTTAAATTAGGGGGACTACAGGCCATTGCAGAATTATTGCAA GTGGACTGTGAAATGTA**C**GGGCTTACTAATGACCACTACAGTA TTACACTAAGACGATATGCTGGAATGGCTTTGACA	1501
	TGTCAAAGCCATTCCAGCATATCGTCTTAGTGTAATACTGTAG TGGTCATTAGTAAGCCC**G**TACATTTCACAGTCCACTTGCAATA ATTCTGCAATGGCCTGTAGTCCCCCTAATTTAAAA	1502
	GAAATGTA**C**GGGCTTAC	1503
	GTAAGCCC**G**TACATTTC	1504
Adenomatous polyposis coli Arg499Term CGA-TGA	TTGCAAGTGGACTGTGAAATGTATGGGCTTACTAATGACCACT ACAGTATTACACTAAGA**C**GATATGCTGGAATGGCTTTGACAAA CTTGACTTTTGGAGATGTAGCCAACAAGGTATGTT	1505
	AACATACCTTGTTGGCTACATCTCCAAAAGTCAAGTTTGTCAA AGCCATTCCAGCATATC**G**TCTTAGTGTAATACTGTAGTGGTCA TTAGTAAGCCCATACATTTCACAGTCCACTTGCAA	1506
	CACTAAGA**C**GATATGCT	1507
	AGCATATC**G**TCTTAGTG	1508
Adenomatous polyposis coli Tyr500Term TAT-TAG	AGTGGACTGTGAAATGTATGGGCTTACTAATGACCACTACAGT ATTACACTAAGACGATA**T**GCTGGAATGGCTTTGACAAACTTGA CTTTTGGAGATGTAGCCAACAAGGTATGTTTTTAT	1509
	ATAAAAACATACCTTGTTGGCTACATCTCCAAAAGTCAAGTTTG TCAAAGCCATTCCAGC**A**TATCGTCTTAGTGTAATACTGTAGTG GTCATTAGTAAGCCCATACATTTCACAGTCCACT	1510
	AGACGATA**T**GCTGGAAT	1511
	ATTCCAGC**A**TATCGTCT	1512
Adenomatous polyposis coli Lys586Term AAA-TAA	GACAAATTCCAACTCTAATTAGATGACCCATATTCTGTTTCTTA CTAGGAATCAACCCTC**A**AAAGCGTATTGAGTGCCTTATGGAAT TTGTCAGCACATTGCACTGAGAATAAAGCTGATA	1513
	TATCAGCTTTATTCTCAGTGCAATGTGCTGACAAATTCCATAA GGCACTCAATACGCTTT**T**GAGGGTTGATTCCTAGTAAGAAACA GAATATGGGTCATCTAATTAGAGTTGGAATTTGTC	1514
	CAACCCTC**A**AAAGCGTA	1515

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TACGCTTTTGAGGGTTG	1516
Adenomatous polyposis coli Leu592Term TTA-TGA	TAGATGACCCATATTCTGTTTCTTACTAGGAATCAACCCTCAAA AGCGTATTGAGTGCCTTATGGAATTTGTCAGCACATTGCACTG AGAATAAAGCTGATATATGTGCTGTAGATGGTGC	1517
	GCACCATCTACAGCACATATATCAGCTTTATTCTCAGTGCAAT GTGCTGACAAATTCCATAAGGCACTCAATACGCTTTTGAGGGT TGATTCCTAGTAAGAAACAGAATATGGGTCATCTA	1518
	GAGTGCCTTATGGAATT	1519
	AATTCCATAAGGCACTC	1520
Adenomatous polyposis coli Trp593Term TGG-TAG	ATGACCCATATTCTGTTTCTTACTAGGAATCAACCCTCAAAAG CGTATTGAGTGCCTTATGGAATTTGTCAGCACATTGCACTGAG AATAAAGCTGATATATGTGCTGTAGATGGTGCACT	1521
	AGTGCACCATCTACAGCACATATATCAGCTTTATTCTCAGTGC AATGTGCTGACAAATTCCATAAGGCACTCAATACGCTTTTGAG GGTTGATTCCTAGTAAGAAACAGAATATGGGTCAT	1522
	TGCCTTATGGAATTTGT	1523
	ACAAATTCCATAAGGCA	1524
Adenomatous polyposis coli Trp593Term TGG-TGA	TGACCCATATTCTGTTTCTTACTAGGAATCAACCCTCAAAAGC GTATTGAGTGCCTTATGGAATTTGTCAGCACATTGCACTGAGA ATAAAGCTGATATATGTGCTGTAGATGGTGCACTT	1525
	AAGTGCACCATCTACAGCACATATATCAGCTTTATTCTCAGTG CAATGTGCTGACAAATTCCATAAGGCACTCAATACGCTTTTGA GGGTTGATTCCTAGTAAGAAACAGAATATGGGTCA	1526
	GCCTTATGGAATTTGTC	1527
	GACAAATTCCATAAGGC	1528
Adenomatous polyposis coli Tyr622Term TAC-TAA	TAAAGCTGATATATGTGCTGTAGATGGTGCACTTGCATTTTTG GTTGGCACTCTTACTTACCGGAGCCAGACAAACACTTTAGCC ATTATTGAAAGTGGAGGTGGGATATTACGGAATGTG	1529
	CACATTCCGTAATATCCCACCTCCACTTTCAATAATGGCTAAA GTGTTTGTCTGGCTCCGGTAAGTAAGAGTGCCAACCAAAAAT GCAAGTGCACCATCTACAGCACATATATCAGCTTTA	1530
	CTTACTTACCGGAGCCA	1531
	TGGCTCCGGTAAGTAAG	1532
Adenomatous polyposis coli Gln625Term CAG-TAG	GATATATGTGCTGTAGATGGTGCACTTGCATTTTTGGTTGGCA CTCTTACTTACCGGAGCCAGACAAACACTTTAGCCATTATTGA AAGTGGAGGTGGGATATTACGGAATGTGTCCAGCT	1533
	AGCTGGACACATTCCGTAATATCCCACCTCCACTTTCAATAAT GGCTAAAGTGTTTGTCTGGCTCCGGTAAGTAAGAGTGCCAAC CAAAAATGCAAGTGCACCATCTACAGCACATATATC	1534
	ACCGGAGCCAGACAAAC	1535
	GTTTGTCTGGCTCCGGT	1536

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenomatous polyposis coli Leu629Term TTA-TAA	TAGATGGTGCACTTGCATTTTTGGTTGGCACTCTTACTTACCG GAGCCAGACAAACACTT**T**AGCCATTATTGAAAGTGGAGGTGG GATATTACGGAATGTGTCCAGCTTGATAGCTACAAA	1537
	TTTGTAGCTATCAAGCTGGACACATTCCGTAATATCCCACCTC CACTTTCAATAATGGCT**A**AAGTGTTTGTCTGGCTCCGGTAAGT AAGAGTGCCAACCAAAAATGCAAGTGCACCATCTA	1538
	AAACACTT**T**AGCCATTA	1539
	TAATGGCT**A**AAGTGTTT	1540
Adenomatous polyposis coli Glu650Term GAG-TAG	GCCATTATTGAAAGTGGAGGTGGGATATTACGGAATGTGTCC AGCTTGATAGCTACAAAT**G**AGGACCACAGGTATATATAGAGTT TTATATTACTTTTAAAGTACAGAATTCATACTCTCA	1541
	TGAGAGTATGAATTCTGTACTTTAAAAGTAATATAAAACTCTAT ATATACCTGTGGTCCT**C**ATTTGTAGCTATCAAGCTGGACACAT TCCGTAATATCCCACCTCCACTTTCAATAATGGC	1542
	CTACAAAT**G**AGGACCAC	1543
	GTGGTCCT**C**ATTTGTAG	1544
Adenomatous polyposis coli Trp699Term TGG-TGA	TGCATGTGGAACTTTGTGGAATCTCTCAGCAAGAAATCCTAAA GACCAGGAAGCATTATG**G**GACATGGGGGCAGTTAGCATGCTC AAGAACCTCATTCATTCAAAGCACAAAATGATTGCT	1545
	AGCAATCATTTTGTGCTTTGAATGAATGAGGTTCTTGAGCATG CTAACTGCCCCCATGTC**C**CATAATGCTTCCTGGTCTTTAGGAT TTCTTGCTGAGAGATTCCACAAAGTTCCACATGCA	1546
	GCATTATG**G**GACATGGG	1547
	CCCATGTC**C**CATAATGC	1548
Adenomatous polyposis coli Ser713Term TCA-TGA	AAGACCAGGAAGCATTATGGGACATGGGGGCAGTTAGCATGC TCAAGAACCTCATTCATT**C**AAAGCACAAAATGATTGCTATGGG AAGTGCTGCAGCTTTAAGGAATCTCATGGCAAATAG	1549
	CTATTTGCCATGAGATTCCTTAAAGCTGCAGCACTTCCCATAG CAATCATTTTGTGCTTT**G**AATGAATGAGGTTCTTGAGCATGCT AACTGCCCCCATGTCCCATAATGCTTCCTGGTCTT	1550
	CATTCATT**C**AAAGCACA	1551
	TGTGCTTT**G**AATGAATG	1552
Adenomatous polyposis coli Ser722Gly AGT-GGT	GGGGCAGTTAGCATGCTCAAGAACCTCATTCATTCAAAGCAC AAAATGATTGCTATGGGA**A**GTGCTGCAGCTTTAAGGAATCTCA TGGCAAATAGGCCTGCGAAGTACAAGGATGCCAATA	1553
	TATTGGCATCCTTGTACTTCGCAGGCCTATTTGCCATGAGATT CCTTAAAGCTGCAGCAC**T**TCCCATAGCAATCATTTTGTGCTTT GAATGAATGAGGTTCTTGAGCATGCTAACTGCCCC	1554
	CTATGGGA**A**GTGCTGCA	1555
	TGCAGCAC**T**TCCCATAG	1556

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenomatous polyposis coli Leu764Term TTA-TAA	TCTCCTGGCTCAGCTTGCCATCTCTTCATGTTAGGAAACAAAA AGCCCTAGAAGCAGAAT**T**AGATGCTCAGCACTTATCAGAAACT TTTGACAATATAGACAATTTAAGTCCCAAGGCATC	1557
	GATGCCTTGGGACTTAAATTGTCTATATTGTCAAAAGTTTCTGA TAAGTGCTGAGCATCT**A**ATTCTGCTTCTAGGGCTTTTTGTTTC CTAACATGAAGAGATGGCAAGCTGAGCCAGGAGA	1558
	AGCAGAAT**T**AGATGCTC	1559
	GAGCATCT**A**ATTCTGCT	1560
Adenomatous polyposis coli Ser784Thr TCT-ACT	TTAGATGCTCAGCACTTATCAGAAACTTTTGACAATATAGACAA TTTAAGTCCCAAGGCA**T**CTCATCGTAGTAAGCAGAGACACAG CAAGTCTCTATGGTGATTATGTTTTTGACACCATC	1561
	GATGGTGTCAAAAACATAATCACCATAGAGACTTGCTGTGTCT CTGCTTACTACGATGAG**A**TGCCTTGGGACTTAAATTGTCTATA TTGTCAAAAGTTTCTGATAAGTGCTGAGCATCTAA	1562
	CCAAGGCA**T**CTCATCGT	1563
	ACGATGAG**A**TGCCTTGG	1564
Adenomatous polyposis coli Arg805Term CGA-TGA	CTCATCGTAGTAAGCAGAGACACAGCAAGTCTCTATGGTGATT ATGTTTTTGACACCAAT**C**GACATGATGATAATAGGTCAGACAT TTTAATACTGGCACATGACTGTCCTTTCACCATAT	1565
	ATATGGTGAAAGGACAGTCATGTGCCAGTATTAAAATGTCTGA CCTATTATCATCATGTC**G**ATTGGTGTCAAAAACATAATCACCAT AGAGACTTGCTGTGTCTCTGCTTACTACGATGAG	1566
	ACACCAAT**C**GACATGAT	1567
	ATCATGTC**G**ATTGGTGT	1568
Adenomatous polyposis coli Gln879Term CAG-TAG	GGTCTAGGCAACTACCATCCAGCAACAGAAAATCCAGGAACT TCTTCAAAGCGAGGTTTG**C**AGATCTCCACCACTGCAGCCCAG ATTGCCAAAGTCATGGAAGAAGTGTCAGCCATTCATA	1569
	TATGAATGGCTGACACTTCTTCCATGACTTTGGCAATCTGGGC TGCAGTGGTGGAGATCT**G**CAAACCTCGCTTTGAAGAAGTTCC TGGATTTTCTGTTGCTGGATGGTAGTTGCCTAGACC	1570
	GAGGTTTG**C**AGATCTCC	1571
	GGAGATCT**G**CAAACCTC	1572
Adenomatous polyposis coli Ser932Term TCA-TAA	TACATTGTGTGACAGATGAGAGAAATGCACTTAGAAGAAGCTC TGCTGCCCATACACATT**C**AAACACTTACAATTTCACTAAGTCG GAAAATTCAAATAGGACATGTTCTATGCCTTATGC	1573
	GCATAAGGCATAGAACATGTCCTATTTGAATTTTCCGACTTAG TGAAATTGTAAGTGTTT**G**AATGTGTATGGGCAGCAGAGCTTCT TCTAAGTGCATTTCTCTCATCTGTCACACAATGTA	1574
	TACACATT**C**AAACACTT	1575
	AAGTGTTT**G**AATGTGTA	1576
Adenomatous polyposis coli Ser932Term TCA-TGA	TACATTGTGTGACAGATGAGAGAAATGCACTTAGAAGAAGCTC TGCTGCCCATACACATT**C**AAACACTTACAATTTCACTAAGTCG GAAAATTCAAATAGGACATGTTCTATGCCTTATGC	1577